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INDICATIONS FOR SURGERY OF THE UPPER GASTROINTESTINAL TRACT*

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AMONG patients suffering from disorders of the upper gastrointestinal tract the problem of whether or not to undertake surgery is most frequently posed by those with peptic ulcer of the esophagus, stomach or duodenum. Less common, but sometimes requiring difficult decision, are cases of diaphragmatic hernia, esophageal varices, cardiospasm and gastritis. Any attempt to establish rigid criteria for surgery in these conditions is thwarted by the myriad combinations of pros and cons that emerge from consideration of any one case. One may, however, establish general indications for abandoning further medical management in favor of the results achievable by surgery.

PEPTIC ULCER

Partial Obstruction

The necessity for surgical intervention in cases of chronic and advanced pyloric obstruction is obvious to all. Conversely, a frequent error committed in the care of patients with ulcer is stubborn medical management in the face of partial obstruction. At times, such an obstruction is moderate in degree but chronically present; at others it manifests itself in acute episodes of gastric retention interspersed with deceptive periods of apparent well-being. In either event the efficacy of medical management is seriously compromised. We believe, in fact, that many of the so-called "intractable" cases of ulcer are so labeled because partial obstruction is either unrecognized or ignored.

The degree of pyloric stenosis is often measured in terms of gastric retention of a barium meal. The amount retained, however, is an index not only of pyloroduodenal stenosis but also of gastric tone and motor power. If tone is good and peristalsis hyperactive, gastric retention may not be noted even in the face of considerable stenosis. For this reason other criteria (Table 1) in addition to radiologic evidence of gastric retention of a barium meal must be used in evaluating the possibility of low-grade pyloric obstruction. If two or more of the findings listed in Table 1 occur in any case of duodenal ulcer surgical treatment appears preferable to continued medical measures.

TABLE 1. *Manifestations of Partial Pyloric Obstruction.**

History	1. Annually recurring symptoms for 5 or more yr., especially if ulcer formerly perforated
	2. Failure of medical regimen formerly effective in controlling symptoms
	3. Vomiting, or anorexia with epigastric fullness increasing during day
Physical examination	4. Clapotage†
Laboratory findings	5. More than 300 cc. of gastric residue found on 2 or more occasions 3 hr. after average evening meal
X-ray findings	6. Gastric retention (5-hr. residue) on 2 or more occasions
	7. Severely deformed and narrowed pyloroduodenal segment

*Two or more of these findings in any patient constitute a sound indication for surgery.

†This very useful sign — a gastric succussion splash — is unjustifiably neglected. The patient lies on his back, and the physician places his hands on the patient's flanks just below the ribs. The patient is then shaken from side to side. Unusual accumulations of gas and fluid produce a splash, which may be audible or palpable. Clapotage obviously may occur in anyone who has just taken fluid or food, but, except when the pylorus is obstructed, it is usually not elicited more than 3 hr. after a meal.

Acute Bleeding

Many hard-and-fast rules have been proposed for the management of acutely bleeding ulcer, but the very abundance of these programs attests to their lack of uniform success. Far preferable is treatment based on a set of principles that provide guidance but are sufficiently flexible to answer the needs of each patient. A set of such principles is given in

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Table 2. Some of the criteria listed carry more weight than others, but no single criterion should be set up as an indisputable argument for or against surgery.

Ironically, the most significant criterion, the rate of bleeding, is probably the most difficult to judge. Nevertheless, one can make an approximation by determining how much transfused blood is necessary to keep the patient out of shock.[1] A rapid rate of bleeding may be assumed if more than 1500 cc. of whole blood is needed per twenty-four hours to prevent the following phenomena:

The mental and emotional manifestations of impending shock, such as anxiety and restlessness.

Peripheral vascular collapse as indicated by pallor and cold, clammy extremities.

Thirst.

A rising pulse. (A persistent tachycardia is less alarming than a pulse that, after stabilization, begins to rise.)

A low or a dropping blood pressure.

Low urine output — less than 500 cc. in twenty-four hours, provided the patient has been drinking or has been given fluid parenterally during this period.

Another means of judging the extent and duration of bleeding is provided by the direct signs of gastrointestinal blood loss. The significance of frank hematemesis is obvious. The bowel movements supply less reliable information, for some patients may continue to bleed without further bowel movements, and some may expel several tarry stools even after bleeding has stopped. Nevertheless, more than one black bowel movement during twenty-four hours in a patient who is being treated in bed should raise the suspicion of further bleeding. On the other hand, in patients having only one stool or less per twenty-four hours, black movements or ++++ tests for occult blood may occur for nearly a week without signifying further blood loss.

In case of doubt there appears to be little harm in putting a tube into the stomach and gently aspirating the gastric contents. If suction is used the negative pressure should not exceed 1 foot of water. Continuous suction in patients with bleeding ulcer may, as a matter of fact, be beneficial in that gastric acid is removed. In some cases, however, suction does not provide totally reliable information since moderate bleeding from a duodenal ulcer may pass entirely downstream.

The hemoglobin, hematocrit and red-cell count are not trustworthy in the evaluation of acute blood loss. Much helpful information is furnished by determinations of blood volume, but repeated measurements of this type are not generally feasible and perhaps are not too accurate in actively bleeding patients. For these reasons clinical criteria rather than hematologic studies must be used as the principal indexes of continued bleeding or its arrest.

Since we consider the location of the bleeding site significant in deciding whether or not to operate, it is implicit that we recommend all necessary maneuvers, including immediate roentgenology or endoscopy, if necessary, to locate the source of bleeding. Identification of a gastric ulcer is a strong indication for immediate surgery since such ulcers often bleed violently and are readily controlled by the surgeon. Conversely, failure to demonstrate the responsible lesion by satisfactory roentgenologic study, particularly in conjunction with endoscopy, should deter

TABLE 2. *Indications for Immediate Operation in Patients with Acute Upper Gastrointestinal Bleeding, Presumably from Peptic Ulcer.*

INDICATION	SIGNIFICANT MANIFESTATIONS		RELATIVE IMPORTANCE
Rapid rate of bleeding	1. More than 1500 cc. of blood needed per 24 hr. to prevent signs of impending shock 2. Hematemesis (more than twice in 24 hr.) 3. Tarry stools (more than 3 in 24 hr.)		++++
Failure of bleeding to stop in 3 days	1. Hematemesis 2. Tarry stools (more than 2 in 24 hr.) 3. Bouts of increased tachycardia or decreased blood pressure 4. Bloody gastric-tube drainage 5. Hemoglobin and hematocrit *falling* in spite of transfusions	After first 48 hr. in hospital	+++
Recurrent bleeding after apparent arrest for 24 hr. or more	1. Hematemesis 2. Sudden reappearance of tachycardia, restlessness, drop in blood pressure and other signs of impending shock 3. Increase in looseness and tarry appearance of stools		+++
Identification of source of bleeding*	1. Gastric ulcer 2. Duodenal ulcer		++++ ++
History of previous severe bleeding†			++
Age over 45			0

*Failure of appropriate studies to demonstrate bleeding site is moderate contraindication to surgery.

†Definitive operation indicated if patient not in shock and seen within 24 hr. of onset of bleeding.

the surgeon, for it is possible that on operation he too will be unable to find the bleeding site or will find such diffuse gastric oozing that he cannot arrest the bleeding successfully short of performing a total gastrectomy.

The age of a patient, in our opinion, is an unimportant criterion of whether or not surgery should be performed. Although many articles differ from this point of view the crucial question has not been answered: If all elderly patients with bleeding ulcers are operated on immediately, is the mortality less than if they are treated selectively? Until it is shown that immediate surgery in such patients reduces the mortality that might be expected otherwise, nothing is gained by the monotonous reiteration of the obvious fact that elderly patients do not tolerate severe illness as well as the young.

A history of one or more previous major hemorrhages in an acutely bleeding patient with known peptic ulcer may be considered an indication for immediate surgery if the patient is in good condition and has been bleeding for less than twenty-four hours. Under such conditions the experienced surgeon need not delay the definitive ulcer operation (that is, partial gastrectomy with or without vagotomy), which ultimately becomes necessary in those with recurrent bleeding.

Interval Operation for the Recurrent Bleeding Ulcer

Repeated episodes of bleeding from peptic ulcer may be considered an indication for elective surgery, but the usual practice of stating that operation is necessary after some arbitrary number of hemorrhages, without qualifications regarding intervals and intensity of bleeding, has little to recommend it. A patient who bled massively twenty years ago, mildly eighteen years ago and massively fifteen years ago may now be entering the hospital with a moderate hemorrhage. These four episodes, however, do not have the same significance as two episodes of massive bleeding occurring within a year. If severe bleeding is defined as that which requires transfusion or that which reduces the hemoglobin level below 50 per cent of its normal value, two such episodes in one year, three within five years or four within ten years may be considered as adequate indications for interval surgery. These criteria may be influenced somewhat by the age of the patient. In an elderly person two severe hemorrhages within three years justify surgery. Even one massive bleeding in a person over sixty, particularly if the bleeding was arrested with difficulty, may be considered a strong indication for interval surgery unless optimal medical control can be maintained.

Intractability

Operation may be considered in a case of duodenal ulcer if all the following conditions exist to indicate that medical treatment has been and will continue to be ineffectual.

Ulcer symptoms occurring intermittently over a period of five years or more.

More than two weeks lost from work annually for three years because of ulcer symptoms.

Exposure to adequate ulcer treatment for a period of at least a year. Adequate treatment includes frequent feedings with interval intake of milk at stated times, frequent use of antacids *between* meals at regular and stated times, intensive use of anticholinergic agents and continuation of the regimen in some form or other during the evening and night. During his asymptomatic periods the patient should be maintained, at a minimum, on regular meals with interval feedings of milk and regular use of anticholinergics. Unless the medical regimen embodies these features it cannot be considered adequate.

The indications for surgery on the basis of intractability should be considered strengthened by a past history of acute perforation, episodes of vomiting or radiologic evidence of a severely deformed pylorus and duodenal bulb. Each of these characteristics suggests that the patient suffers from low-grade pyloric obstruction, an important cause, in our opinion, of so-called intractability.

A major problem is presented by apparently intractable symptoms in a patient who has been offered an adequate regimen but who will not or cannot observe the required measures. So many patients fall into this category that the cliché, "it is the patient, not the ulcer that is intractable," has become a clinical axiom. As a corollary to this statement the belief has gradually evolved that the patient who will not follow treatment but who at the same time complains bitterly of pain is apt to prove a poor candidate for surgical therapy because he is particularly prone to all varieties of post-gastrectomy complaints. To some extent this is true, for the man who complains about everything will not be radically changed by operation. On the other hand, it appears from observations made by Dr. Thomas Warthin[2] at West Roxbury and Dr. John C. Bullard[3] at Cushing Veterans Administration hospitals that at least half the so-called intractable patients respond brilliantly to definitive ulcer surgery. We therefore suggest that operation be carried out for intractability if the criteria listed above apply, disregarding, except in the rare case, the patient's emotional make-up and his lack of adherence to any prescribed medical regimen. Insisting upon "just one more try of medical treatment" in cases of this type is almost invariably fruitless, whether or not formal psychotherapy is added to standard medical measures.

It is sometimes argued that older patients should be operated on more readily for intractability than younger ones because the aged tend to be less susceptible to medical management and the younger ones are "too young to have their stomachs re-

moved." This appears fallacious to us since the young patient with duodenal ulcer who satisfies the criteria for intractability faces many years of suffering if he does not receive surgical relief. We do not believe that the age of the patient should influence the decision, except when a person is so elderly as to render an operation hazardous. Other complicating disorders such as chronic renal disease, especially that based on long-standing alkali ingestion, and coronary insufficiency are actually indications for rather than against surgery provided that the patient's operative risk is not extreme. If not treated surgically, the intractable ulcer tends to aggravate the renal or cardiac disease.

Acute Perforation

Treatment of the acutely perforated ulcer remains primarily a surgical problem. It is apparent, however, that conservative management with constant gastric suction, no oral intake, parenteral maintenance of electrolytic balance and intensive use of antibiotics can be successful and is preferable to surgical therapy under certain specific circumstances. Surgery is indicated for patients seen within twenty-four hours of perforation. If the patient is not seen until forty-eight hours or more after perforation, conservative management is usually the better course. For patients seen between twenty-four and forty-eight hours after perforation the decision must be based on individual factors such as the general condition of the patient, the apparent magnitude of the perforation, the degree of paralytic ileus and evidence of persistent leakage through the perforated area. Although conservative management is satisfactory for tiding over the patient seen late after his perforation, surgical drainage of residual intraperitoneal abscesses is frequently necessary at a later stage.

Gastric Ulcer

Few issues are so controversial as the question whether or not to operate for gastric ulcer. If the surgeon believes that there is no clinical means of differentiating benign from malignant ulcers he should operate immediately on every gastric ulcer, since over-all figures show that 10 to 15 per cent of surgically treated gastric ulcerations that appear radiologically benign are actually malignant, whereas the mortality of operation for a gastric cancer is half as great. This ratio is tempered, however, by the fact that clinical judgment can improve on random choice in differentiating malignant and benign ulcers. The criteria on which clinical judgment relies are as follows:

Age and sex. Although a young woman can have gastric cancer the statistical chances are against it. Therefore, the younger the patient, the more one is justified in attempting medical therapy before undertaking operation, especially if the patient is a woman.

Radiologic characteristics of the ulcer. Some of the nuances of gastric motility and mucosal relief that permit the expert radiologist to render a valuable opinion concerning the nature of a gastric ulcer cannot be discussed by us. All physicians, however, may consider some of the grosser features of an ulcer and its position in the stomach. Many believe that all ulcers on the greater curvature are malignant and that prepyloric ulcers are more likely to be malignant than those lying elsewhere on the lesser curvature and its adjoining walls. These beliefs, however, particularly the incrimination of ulcers in the prepyloric area, require revision. Several careful studies have shown that prepyloric ulcers appearing grossly benign on radiologic examination are no more likely to be malignant than ulcers elsewhere in the stomach.[4, 5] This is certainly true of our own experience. Parenthetically, it may be added that ulcers in the pyloric canal are usually benign and should be treated as duodenal ulcers. Unfortunately, pyloric ulcers may so deform the normal landmarks that the exact location of the lesion is difficult to determine.

It has become clear that ulcers on the greater curvature do not necessarily mean neoplasm.[6] At present, however, not enough is known concerning these relatively infrequent ulcers to permit an accurate statement about the incidence of cancer. Until this information is available, it is recommended that the location of an ulcer on the greater curvature be considered a strong indication for operation.

Ulcers in the cardia probably manifest no unusual tendency to malignant degeneration, but both benign and neoplastic lesions in this area often escape the radiologist's notice and may not be discovered until the process becomes quite extensive. The high position of a cardiac ulcer also accounts for the fact that surgical removal sometimes requires total gastrectomy, a necessity that may be taken as a mild reason in favor of medical treatment.

Antral spasm associated with an ulcer lying proximal to the antrum, mucosal folds radiating centripetally toward the niche and an incisura opposite the ulcer have been taken as indications of a benign process. These criteria, however, may prove treacherous, particularly in patients with recurrent gastric ulceration. With respect to the appearance of the ulcer itself, deep penetrating lesions that project like the tip of a finger from the lesser curvature are more likely to be benign, whereas flat, plaque-like defects are more suggestive of neoplasm. The actual size of the ulcer is of no significance.

Deformity of the duodenal cap indicative of a healed duodenal ulcer may be taken as weak evidence that an associated gastric ulcer is benign. An active duodenal ulcer crater is much stronger evidence against gastric cancer.

Recurrence of ulcer. As far as the possibility of neoplasia is concerned the recurrence of an ulcer may be given two entirely different interpretations. It may be argued, on the one hand, that it is unlikely for a neoplastic lesion to disappear and recur over a period of years. On the other hand, if it is possible for a neoplasm to develop in a field prepared by a recurring benign ulcer, recurrence may be considered a dangerous sign. The bitter pathological debate whether or not a recurring ulcer that eventually proves to be malignant contains neoplastic cells from its very inception, has not been resolved. From the clinical point of view, however, it must be emphasized that ulcers that begin and continue for three to six years with the manifestations of benignancy may eventually turn out to be malignant. In some cases a carcinoma in situ is found at the base of such a chronically recurring ulcer. These facts indicate that recurrence per se cannot be taken as a strong argument either for or against neoplasm. It is our opinion that a recurrent ulcer, particularly in males, should be viewed with suspicion as a lesion that either is or may become malignant. In females the implications of recurrence are less serious. In any event it may be argued with some justification that a recurrent ulcer, regardless of its nature, provides evidence for the failure of medical therapy. For these reasons we recommend surgery for males who have had one recurrence of gastric ulcer and for females who have had two. It should be noted that a "recurrence" does not invariably imply complete healing of the ulcer between the two symptomatic periods. In a number of cases it is probable that the patient is relieved symptomatically and the ulcer heals sufficiently to escape radiologic detection, but the lesion may actually never disappear completely.

Response to medical management. If the response to medical management is to be taken as a criterion, management should be carried out as intensively as possible and should embody the measures that constitute adequate treatment of duodenal ulcer. In spite of the fact that gastric acidity may not be elevated in patients with gastric ulcer, anticholinergics should be used intensively. If possible bed rest should be included in the therapeutic program.

Many large ulcers, including those that are benign, do not disappear in three weeks. We therefore suggest that the ulcer should be at least 50 per cent smaller at the end of three weeks of intensive medical management. If this is so another three-week period of medical management may be attempted. At this time the ulcer either should have disappeared or should be no larger than a tiny pit surrounded by evidences of scar formation. The effects of subsequent medical therapy should be checked at intervals of three and six months thereafter to make sure that healing has been maintained. This step is often neglected but is essential if gastric ulcers are to be managed medically.* If healing and disappearance of the gastric ulcer do not measure up to these standards surgery is advisable. Actually, many benign ulcers will be resected if one adheres to these arbitrary rules, but any ulcer that is so resistant to medical management that it does not disappear or recurs within a seven-month interval probably requires surgical treatment regardless of its morphologic characteristics.

Bleeding. Bleeding continuing from gastric ulceration in spite of medical therapy is a strong indication for surgery.

Special procedures. Examination of the gastric contents for neoplastic cells, gastroscopic examination and studies of gastric secretion are helpful in differentiating benign from malignant gastric ulcers if these procedures are carried out by highly trained personnel with unusual facilities at their disposal. Examination of the exfoliative cytology of the stomach by a hospital that does not have specialized facilities and gastroscopy performed by a man who seldom uses this procedure are of little use. Routine gastric analysis after histamine stimulation is often recommended for the detection of gastric anacidity but has proved unreliable in our experience. In some patients with benign gastric ulcers only elaborate secretory studies employing insulin-induced hypoglycemia as a stimulus are adequate to demonstrate the stomach's ability to secrete free acid. From a practical point of view these specialized procedures are consequently useful to the extent that they are available at a high level of proficiency. Frequently, the decision whether or not to operate in a case of gastric ulcer has to be made without their help.

Gastritis

Three types of gastritis may warrant gastrectomy: gastritis that causes serious bleeding, giant hypertrophic gastritis and gastritis that mimics cancer.

Although not common, gastritis is a definite cause of repeated major gastrointestinal hemorrhage. Sometimes the responsible lesion is localized; more often it is diffuse. If a localized lesion is unequivocally identified by an experienced gastroscopist (radiologic examination is of limited value in these cases), partial gastrectomy is justified in a patient who has had two or more bleeding episodes. In cases of diffuse gastritis or if the responsible lesion defies exhaustive diagnostic procedures and is considered to be gastritis merely by exclusion or inference, the problem is much more complex. Partial gastrectomy, even that including two thirds

*Counting the original radiologic examination, the program outlined calls for a total of five x-ray examinations of the stomach in the course of eight months. If a complete so-called gastrointestinal series is carried out in each case the expense is formidable. There is no reason, however, for performing a complete gastrointestinal examination at each follow-up observation. It is entirely sufficient for the radiologist to make fluoroscopic observations and to take spot films limited to the area where ulceration was known to exist. Such examinations should cost no more than $10 or $15 each. Some radiologists will object to this suggestion, but it is essential for proper care of many gastrointestinal conditions that repeated examinations be limited in both scope and expense.

or more of the stomach, may not prevent further hemorrhage from the gastric remnant, and the only procedure giving reasonable assurance of success is total gastrectomy. Although radical, this operation appears indicated if the patient has had three major hemorrhages and gastroscopy definitely reveals a diffuse gastritis. Even if the diagnosis of diffuse gastritis cannot be established, total gastrectomy has to be considered in a patient who has bled violently on three occasions, provided that: the source of the bleeding has been located in the upper gastrointestinal tract by a history of hematemesis, gastric aspiration or a string test; exhaustive radiologic, endoscopic and hepatic-function studies have not revealed any cause for bleeding; sources of extragastric blood loss are not found at laparotomy; and the gastric mucosa is directly examined for a localized process at the time of operation by insertion of a sigmoidoscope through a gastrostomy.[7] If these conditions are fulfilled it may be assumed that the stomach is the source of bleeding.

Giant hypertrophic gastritis is a condition that distorts the mucosal lining of the stomach to such a degree that radiologic identification of superimposed ulceration or neoplasm is difficult. Although statistical evidence is lacking individual case reports suggest that the lesion is occasionally precancerous. Finally, the patient may suffer considerable distress, which responds only moderately to the usual type of antiulcer therapy. For these reasons, partial or total gastrectomy has been recommended. We believe, however, that giant hypertrophic gastritis does not warrant surgery unless hemorrhage supervenes, symptoms are uncontrollable or changing radiologic or gastroscopic characteristics suggest an increasing possibility of neoplasia.

Inflammatory deformities of the antrum sometimes cannot be differentiated from cancer by any diagnostic means. In cases of real doubt it seems best to attack all such lesions surgically, for the immediate mortality and morbidity incurred by removal of the distal portion of the stomach are not great.

Polyps

The demonstration of a polyp in the esophagus, stomach or duodenum is an indication for surgery. Unless the lesion is removed malignant degeneration will be a constant cause of concern to both the patient and the physician. The chance that a polyp may be responsible for hemorrhage or obstruction is further reason for its surgical removal.

Cardiospasm

Some patients with cardiospasm either are asymptomatic or can be kept comfortable with diet and general support. These measures, however, are relatively ineffective and should be supplemented with esophageal dilatation if the patient is distressed by eating, suffers easy regurgitation on lying down or can be maintained only on a very restricted diet. Dilatation should be used readily and without delay, not only for the relief that it affords to most patients but also in an effort to prevent the massive stretching of the esophagus and pulmonary complications that may ensue if the disease progresses unchecked. Periodic bouginage often accomplishes dilatation, but in our experience a more satisfactory result is obtained with a hydrostatic or pneumostatic bag carefully placed and used by a thoracic surgeon well versed in the procedure.

In some patients one dilatation appears to suffice; in others the procedure must be repeated at unpredictable intervals. In general, however, repeated and not too-long-postponed dilatations are vastly preferable to any surgical procedure. As recent studies have shown cardiospasm is not a disorder confined to the distal esophagus but is a motility derangement of nearly the entire organ. Consequently, any surgical procedure that removes or by-passes the narrowed segment at the same time permits ready gastric reflux into an esophagus that does not have the motor power to expel the irritating material. The result is inflammation, ulceration and hemorrhage, the total clinical picture often being more distressing than the cardiospasm for which the operation was undertaken.

In an effort to lessen esophageal stasis without promoting gastric reflux, surgeons have increasingly used the Heller operation, which merely sections the muscle of the perpetually contracted esophageal segment.[8] Sometimes this procedure is technically not feasible; sometimes the results are disappointing, but at present it is the preferred operation if surgery becomes necessary. This point is reached when dilatations are unsuccessful and the patient loses weight, suffers from progressive dysphagia or has signs of pulmonary complications.

Diaphragmatic Hernia and Esophagitis

Hernias of the esophageal hiatus of the diaphragm are usually classified according to their anatomic characteristics. In considering the indications for surgical intervention, however, we believe that a clinically more useful classification is to divide these hernias into two groups: those with and those without esophagitis. An associated esophagitis calls for ready surgical intervention. In other diaphragmatic hernias surgery is indicated only under exceptional circumstances.

Hernia with Esophagitis

Esophagitis may complicate the sliding or short-esophagus type of diaphragmatic hernia. In this type the stomach on radiologic examination is seen to project into the thoracic cavity like a tent, its peak supported by an apparently shortened esophagus. This configuration is believed to permit ready reflux of gastric contents into the lower esophagus,

which is thereby exposed to peptic inflammation, ulceration and stenosis. If the patient has abundant gastric acidity, as in associated duodenal ulcer, the danger of esophageal irritation by gastroesophageal reflux is obviously heightened.

Once peptic esophagitis is chronic and well established the pain and dysphagia respond poorly to medical management. If the narrowed esophageal lumen is dilated or resected retrograde reflux as well as swallowing is facilitated. Consequently, it appears reasonable to correct the underlying anatomic defect early in the course of the disorder before permanent narrowing of the esophageal lumen takes place.

One attack of esophagitis associated with hiatal herniation may respond to medical management, especially if the episode is precipitated by gastrointestinal intubation. Once a second attack has occurred spontaneously, however, surgical repair of the hernia appears indicated, provided that the patient suffers pain or dysphagia and esophageal damage can be demonstrated radiologically. If, as is often the case, the patient also has or has had a duodenal ulcer, operation should certainly not be delayed.

A certain number of patients with esophagitis are first seen when the disease is so far advanced that it will no longer respond to repair of the hernia alone. In these cases resection of the contracted segment or at least mechanical dilatation after the hernial repair may be necessary.

Hernias

A vast number of diaphragmatic hernias of all types — paraesophageal (parahiatal), sliding (short esophagus) and composite forms — exist without associated disease of the esophagus. Since these hernias are very common, they have been blamed for a great variety of thoracoabdominal symptoms. Actually, their very prevalence indicates that hernias will be found in many patients merely on the basis of chance, and a diaphragmatic hernia should not be held responsible for a patient's complaints merely because no other cause can be found. The belief that diaphragmatic hernias are a common source of blood loss is, for example, based on the observation that diaphragmatic hernias are found often in patients with unexplained gastrointestinal bleeding. Diaphragmatic hernias, however, are often found in elderly people, and ascribing the bleeding to the hernia is a weak correlation based on no more than circumstantial evidence. As a matter of fact, direct evidence, such as identification of a bleeding point in a hernia, is rarely available.[9] Since we believe that diaphragmatic hernias are frequently blamed for difficulties arising from other causes, surgical treatment is not recommended unless a hernia has been identified unquestionably as the source of any of the following major complications: intermittent esophageal obstruction, respiratory disorders, perforation, strangulation, bleeding and severe distress not attenuated by intensively applied medical measures.

If a hernia produces acute dysphagia or respiratory embarrassment, or if it perforates or strangulates, the need for surgical management is self-evident. If a patient with a diaphragmatic hernia loses blood acutely or chronically from the gastrointestinal tract it is essential to rule out other, more common sources of such bleeding and to investigate the role of the hernia by endoscopic examination, gastric aspiration or the string test. Perhaps the most difficult problem is presented by patients who have diaphragmatic hernias and also vague symptoms in the lower thorax or upper abdomen. In these cases the decision whether or not to operate must be based principally on clinical grounds; the size of the hernia or the ease with which it slips in and out of the thoracic cavity is of secondary importance. Belching, epigastric pressure, full sensations after heavy meals and intermittent heartburn of mild degree are not sufficient reasons for surgical repair of a diaphragmatic hernia since these symptoms are common enough in people with a perfectly normal esophageal hiatus. Surgery does appear indicated, on the other hand, if a patient with diaphragmatic hernia, in spite of maintaining a semiupright position at night, is so distressed that he cannot sleep, or if he suffers chronic and incapacitating distress after meals in spite of conscientious efforts to limit the size of his food intake.

Diverticula

Diverticula in the upper gastrointestinal tract occur in the esophagus, the gastric cardia and commonly in the descending and transverse portions of the duodenum. Except for the so-called Zenker diverticulum at the upper end of the esophagus one should beware of surgery for these radiologically impressive but clinically unimportant abnormalities. Diverticula in the upper gastrointestinal tract occur so frequently that they are often found in patients with digestive disorders, but they are almost never the cause of the trouble. To be sure, a small number of these diverticula lead to obstruction, hemorrhage, jaundice, ulceration and pancreatitis, but these cases are the exception. As a general rule, one will make many fewer mistakes by assuming that all these diverticula are harmless than by incriminating them when pain, hemorrhage or other symptoms cannot easily be explained otherwise.

Esophageal Varices

The efficacy of portacaval or splenorenal shunts in controlling hemorrhage in some cases of esophageal varices is undoubted. The value of arterial ligation is questionable.[10] In this discussion consequently, the indications for the various types of shunting procedures are considered.

Any patient who has radiologically or endoscopically demonstrated esophageal or gastric varices and who has suffered at least one massive bleeding episode is a candidate for a shunting operation. We do not believe that the mere demonstration of varices without at least one hemorrhage is sufficient indication for the difficult surgery that is entailed. The contraindications to surgery are severe liver disease or acute bleeding of sufficient magnitude to render the patient a poor risk for lengthy operations. According to these criteria all patients who suffer from nonmalignant, extrahepatic obstruction of the portal circulation should have shunting procedures once they have had a major hemorrhage.

There is no uniformity of opinion about the severity of liver disease that should contraindicate a shunting procedure. Linton's[11] criteria, which are based on extensive experience, appear somewhat too demanding since they tend to deprive many cirrhotic patients of the benefit of a shunting procedure. Hence, although cirrhotic patients have a mortality risk of about 20 per cent, more liberal criteria may be proposed, the risk being more than overbalanced by the nearly 100 per cent mortality incurred if nothing is done.

Criteria for choosing cirrhotic patients suitable for shunting operations are usually expressed in terms of liver-function tests, but clinical phenomena are apt to provide a better index of operability. Thus, a drowsy patient who will not eat is a poor risk irrespective of his liver-function tests, and conversely a patient with no ascites or edema and with excellent appetite is a good operative risk even though his bromsulfalein retention is 35 per cent. Table 3 presents a list of the clinical and laboratory criteria used by us in determining whether a cirrhotic patient with esophageal varices is suitable for a shunting type of operation.

TABLE 3. *Criteria of Risk of Shunt Operation for Esophageal Varices.**

Clinical Criteria	Laboratory Criteria						
	Bromsulfalein retention†	Cephalin flocculation	Icteric index	Thymol turbidity	Prothrombin concentration‡	Serum albumin	Cholesterol esters
	%	*24 hr.*	*units*	*units*	%	*gm. /100 cc.*	%
Anorexia, nausea, vomiting Progressive tissue wasting Severe ascites Marked edema (more than + pitting) Frank jaundice Central-nervous-system symptoms (drowsiness, lethargy, restlessness & confusion)	Above 25	More than +++	Above 25	Above 8	Below 40	Below 2.5	Below 30

*Occurrence of 2 criteria suggests mortality risk of 20–40 per cent; if 3 or more present operation is desperate measure.

†5 mg. per kilogram of body weight (45-min. sample).

‡After 10–20 mg. of vitamin K intramuscularly.

Management of Acutely Bleeding Patients

The patient with nonmalignant extrahepatic portal obstruction who is bleeding acutely is best managed by conservative means, including multiple transfusions and balloon tamponade. These patients almost invariably recover from such acute episodes and can be treated surgically once they have recovered from their acute blood loss.

The cirrhotic patient acutely bleeding from varices presents an entirely different problem. Although the bleeding may temporarily stop, either spontaneously or with the aid of balloon tamponade, hemorrhages may recur after deflation of the balloon and, more discouragingly, death from liver failure frequently supervenes in spite of temporary arrest of the bleeding. Such patients are poor surgical risks, but their prognosis on continued medical therapy is equally discouraging. For patients of this type direct ligation of the esophageal and gastric varices by a transthoracic approach has been recommended and has proved successful in a number of cases.[11, 12] Unfortunately, deaths from liver failure may take place in spite of successful ligation of the bleeding vessels. The usefulness of direct ligation of the varices in an acutely bleeding patient with cirrhosis is still undetermined, but it is suggested that the procedure may be used in the presence of bleeding after twenty-four hours of hospital treatment, provided that the patient is not semicomatose or irrational, does not have massive ascites and has a serum bilirubin of less than 5 mg. per 100 cc.

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HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY*

Report of a Case Confused with the "Burnett Syndrome"

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IN 1949 Burnett et al.[1] reported a series of 6 cases characterized by hypercalcemia without hypercalcuria or hypophosphatemia, calcinosis and renal insufficiency. In addition the patients gave a history of prolonged or excessive intake of absorbable alkali and milk and showed clinical improvement on a low-calcium diet. Autopsy was performed in only 1 case, no parathyroid tissue being found. Histologic section in another case was reported as showing "hyperplasia of chief and oxyphil cells characteristic of secondary hyperparathyroidism."

A review of the literature revealed no subsequent case reports with autopsy findings. Clinically and morphologically the following case was at first confused with the syndrome reported by Burnett and his associates. It is a significant case in that it demonstrates the important modifications that renal insufficiency may produce in the chemical picture of hyperparathyroidism caused by a parathyroid adenoma.

CASE REPORT

J. E. P., a 25-year-old man, was first seen on October 14, 1950, because of hematemesis of 24 hours' duration. He stated that the illness began 5 years previously, when epigastric discomfort relieved by food and milk developed. He was treated with unknown medications and diet, with satisfactory improvement. However, the symptoms returned in 1948 and a gastrojejunostomy was performed in another institution. He was asymptomatic until the present complaint, but during this interval consumed "1 or 2 gallons of milk daily" *(sic)*. There was no history of excessive ingestion of absorbable alkali.

Physical examination revealed a mentally retarded man who was quite pale. There was a well healed midepigastric scar. The neck was supple and free of nodules. Ophthalmologic examination disclosed calcified areas in the hyaloid fossa just posterior to the lens. There were also small crystalline deposits in the palpebral tissue and the bulbar conjunctivas. No other significant positive findings were recorded.

Examination of the blood showed a red-cell count of 2,800,000, with a hemoglobin of 6.5 gm. per 100 cc. The urine had a maximum specific gravity of 1.010, and the sediment contained 10–20 white cells per high-power field (centrifuged) and, on infrequent occasions, a trace of protein. The Sulkowitch test was negative, the patient being on a neutral, low-calcium diet. Twenty-four-hour urine calcium excretions were not determined. The carbon dioxide combining power of the blood was 16.7 milliequiv. per liter. The serum calcium level, over a 2-month period ranged between 14.1 and 17.4 mg., and the serum phosphorus between 3.5 and 8.1 mg. (average 5.3) per 100 cc. The blood nonprotein nitrogen ranged from 49 to 81 mg. per 100 cc. The serum alkaline phosphatase averaged 5.1 Bodansky units (3.9 to 7.5). A stool guaiac test was positive. X-ray study of the upper gastrointestinal tract revealed a normally functioning gastroenterostomy. The duodenal bulb was persistently deformed and irritable, with a large pseudodiverticulum of the inferior portion. No definite ulcer crater could be demonstrated. The radiologic survey was repeated 4 months later, and the findings were similar. No renal calculi or calcification could be demonstrated; retrograde pyelograms were considered normal. Bone surveys were not revealing.

It was concluded that the prognosis was poor with persistent hypercalcemia unless the disease was amenable to surgery. On December 15 an exploration of the parathyroid glands was performed. The right inferior, left inferior and a portion of the left superior parathyroid glands were removed. The pathological report was "chief-cell hyperplasia of the parathyroid glands." At discharge on December 21 the serum calcium was 14.6 mg., the serum phosphorus 4.1 mg., the serum alkaline phosphatase 5.7 Bodansky units and the blood nonprotein nitrogen 42 mg. per 100 cc.

On January 9, 1951, the patient was seen in the Outpatient Department and was found to be asymptomatic. The serum calcium and phosphorus were 12.8 and 4.8 mg. per 100 cc. respectively. The blood nonprotein nitrogen was 68 mg. and the serum total protein 5.8 gm. per 100 cc.

On February 5 the patient was readmitted to the hospital because of nausea and vomiting of 48 hours' duration. One week before this admission he began to have black stools. The physical examination was not significant except for a blood-pressure elevation (170/110) for the 1st time.

The stool guaiac test was positive. The urine had a maximum specific gravity of 1.009, and the sediment contained 10–20 white blood cells per high-power field (centrifuged specimen). The Sulkowitch test was ++, with a control of +. *Pseudomonas aeruginosa* was found on culture of the urine. The intravenous phenolsulfonephthalein test showed 20 per cent excretion of the dye in 2 hours with adequate urine output. The red-cell count was 3,400,000, with a hemoglobin of 10 gm. per 100 cc. The blood nonprotein nitrogen was 51 mg. per 100 cc., and the carbon dioxide combining power 19.2 milliequiv. per liter. The serum calcium was 15.7 mg., the phosphorus 4.7 mg., and the alkaline phosphatase 5.3 Bodansky units per 100 cc.

The patient was placed on a regimen of milk and cream every hour in addition to atropine and phenobarbital. Gastric aspirations were done twice daily, the gastric residual volume decreasing over the hospital stay from 475 to 60 cc. The stools became free of blood, and he was discharged on a bland diet.

On April 6, 1952, he was readmitted to the hospital because of nausea, emesis, severe constipation and loss of weight of 3 months' duration. He also had abdominal pain and vomited blood.

Physical examination revealed an acutely and chronically ill, markedly dehydrated man with a pulse of 100 and a blood pressure of 90/50. There were fine, moist rales at both lung bases, the abdomen was tender, and there was + pitting edema of the lower extremities.

The blood studies revealed a carbon dioxide combining power of 14 milliequiv. per liter and serum calcium of 10.3 mg., phosphorus of 6.1 mg. and nonprotein nitrogen of 273 mg. per 100 cc.

The patient was given fluids intravenously and calcium gluconate for tetany, in spite of the calcium level. His condition became progressively worse, and he died less than 24 hours after admission. The final clinical diagnoses included Burnett's syndrome, chronic pyelonephritis, renal acidosis and parathyroid hyperplasia.

At autopsy the body was that of a well developed, poorly nourished man appearing about the stated age of 28 years. He was 75½ inches tall and weighed approximately 150 pounds. Externally, there were well healed scars on the neck and abdomen. The pleural, pericardial and peritoneal cavities were free of excess fluid, and the surfaces smooth and glistening. There were numerous dense adhesions about the upper lobes of the lungs and in the right upper quadrant of the abdomen.

The heart weighed 480 gm. The right ventricle was 0.4 and the left 1.7 cm. in diameter. The coronary arteries contained

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small, yellow, nonulcerated plaques occluding less than 25 per cent of the lumen. The proximal circumflex branch of the left coronary artery was filled with 2 pink, granular masses that completely occluded the lumen. The thoracic and abdominal aorta contained numerous, nonulcerated, intimal atherosclerotic plaques.

The upper air passages were clear. The right lung weighed 1370 gm., and the left 1500 gm. The lung substance was defi-

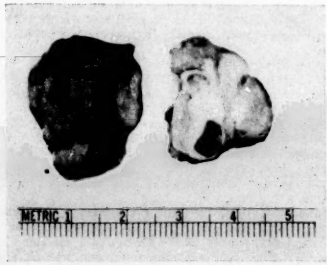

FIGURE 1. *Photograph of the External and Cut Surface of the Adenoma Located in the Superior Mediastinum at Autopsy.*

nitely firm and cut with ease, exuding a frothy, red fluid. There were no focal lesions.

The mucosa of the stomach was intact, and the pylorus was patent. Projecting medially from the first portion of the duodenum and overlying the pancreas was a saccular outpouching, which was 3 cm. in depth. The mucosa of this structure was smooth, and the adjacent tissue was firm. There was a well

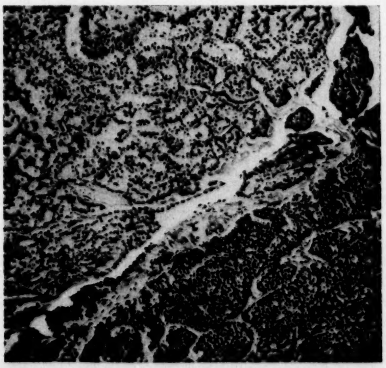

FIGURE 2. *Photomicrograph of the Parathyroid Adenoma, Showing Alveolar Arrangement of Water-Clear Cells in the Upper Left and Cords of Chief and Transitional Cells in the Lower Right (Hematoxylin and Eosin Stain X75).*

healed, patent, posterior gastrojejunostomy scar. No ulceration of duodenal mucosa was found. The external surface of the small intestine had numerous subserosal gas-filled cysts varying from 0.1 to 0.5 cm. in diameter. The liver weighed 2540 gm. but was grossly not remarkable. The gall bladder and biliary ducts were patent. The pancreas weighed 150 gm. and was free of focal lesions.

The right and left kidneys weighed 170 and 220 gm. respectively. The capsules of both organs stripped with some difficulty, exposing a finely and coarsely granular surface. The organs were firm, and scattered throughout the cortex and medulla were numerous hard, gritty, yellow deposits roughly 0.1 cm. in diameter. The left renal pelvis was slightly dilated.

The spleen, which weighed 280 gm., had several irregular areas of capsular opacity, the largest being 4 cm. in greatest diameter. On section the white pulp was obscured.

The perithyroid tissue was dense, and no parathyroid glands as such could be identified. However, in the superior mediastinum, posterior and slightly inferior to the left sternoclavicular joint, there was a yellow-gray discrete, lobulated mass weighing 6 gm. (Fig. 1). On section it was composed of firm, gray-white tissue containing several clear, fluid-filled cysts measuring up to 0.5 cm. in greatest dimension.

Microscopical examination of the heart revealed focal areas of fibrosis and hyalinization throughout the myocardium. In

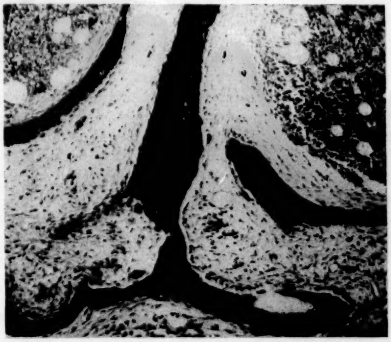

FIGURE 3. *Photomicrograph of Vertebral Bone, Showing Osteitis Fibrosa (Hematoxylin and Eosin Stain X75).*

one area there were focal deposits of calcium. Study of the coronary arteries demonstrated atherosclerotic changes in the intima and calcific deposits in the media, in addition to a recent thrombus in the circumflex branch of the left coronary artery. Sections of the aorta disclosed similar atherosclerotic changes, with calcification.

Many of the pulmonary alveolar walls were thickened by fibrous tissue and contained an exudate composed predominantly of lymphocytes. There were also focal deposits of calcium.

There were focal calcium deposits in the gastric mucosa. The duodenal diverticulum was not remarkable. Minimal central hyperemia was observed in the liver.

The renal capsules were irregularly thickened by focal collections of fibrous tissue. There was also an increment of fibrous tissue in the interstitial tissue. Throughout all sections there was an exudate composed predominantly of lymphocytes. There were also scattered deposits of calcium, principally in the proximal convoluted tubules. The glomeruli were either hypercellular or surrounded by fibrotic capsules. Many of the tubules were atrophic and replaced by fibrous tissue, whereas others were dilated and lined by hypertrophic epithelium. The smaller arteries and arterioles were uniformly thickened by subintimal fibrous tissue.

Sections of the superior mediastinal mass were composed of parathyroid tissue showing considerable variation in cell type (Fig. 2). In some areas there were uniform sheets of chief cells, whereas other areas were composed of alveolar collections of transitional cells and occasional water-clear cells. There were no oxyphil cels. The cystic spaces contained a pink, proteinaceous material whose appearance was similar to that of thyroid colloid.

The vertebral-marrow spaces were widened owing to an increment in fibrous tissue (Fig. 3). There was an increase in osteoblasts and osteoclasts, with a diffuse reduction in both cancellous and compact bone. There was no evidence of metastatic calcification in the thyroid gland.

With these findings the following final anatomic diagnoses were made: solitary parathyroid adenoma of the mediastinum, mixed-cell type; chronic pyelonephritis, with nephrocalcinosis; osteitis fibrosa involving the vertebral bone marrow; metastatic calcification of the stomach, lungs and heart; chronic pneumonitis, probably uremic in origin; myocardial hypertrophy; atherosclerosis and medial calcification of the coronary arteries; recent thrombosis of the circumflex branch of the coronary artery; and focal myocardial fibrosis.

Discussion

Clinically, this patient demonstrated six of the nine criteria of the Burnett syndrome. He did not satisfy three criteria: there was a tendency to acidosis rather than alkalosis, no clinical improvement on a low-calcium diet was demonstrated and there was no history of excess intake of absorbable alkali. A review of the original surgical material from this patient revealed that the parathyroid tissue was atrophic and certainly not hyperplastic (Fig. 4). There is little information on the subject of parathyroid atrophy or the histologic appearance of the remaining parathyroid glands in patients with parathyroid adenoma. In this case there was an absolute decrease in the number and size of the cell cords associated with an increase in loose interstitial connective tissue and fat. Drake et al.[2] reported 2 cases of idiopathic hypoparathyroidism in which the parathyroid glands were almost completely replaced by fat; in 1 case a few recognizable parathyroid cells remained.

Hyperparathyroidism is primarily due to parathyroid adenoma in approximately 80 per cent of the cases. According to Woolner and his co-workers[3] these neoplasms show considerable variation in cell type, size of cells and nuclei and pattern. Of the 115 adenomas described by these authors 33 were classified as mixed in cell type.

The primary findings in hyperparathyroidism are hypercalcemia, hypercalcuria and hypophosphatemia. In addition there may be renal stones or nephrocalcinosis, osteitis fibrosa generalisata and an elevated serum alkaline phosphatase. The excess dietary intake of calcium in the case reported above probably prevented a drain on bone calcium and thus did not result in clinical osteitis fibrosa. For the same reason the alkaline phosphatase was not increased. However, during the terminal months the patient was unable to ingest large quantities of milk owing to increasing anorexia, nausea and vomiting. Finally, osteitis fibrosa developed as a result of either low-calcium intake combined with hyperparathyroidism or increasing acidosis caused by renal failure. It is also possible that the normal serum phosphorus was due to increased intake or renal retention, or both. It is interesting that while he was temporarily on a low-calcium diet during the second hospital admission, the serum phosphorus decreased and the serum calcium increased. This was associated with a slight rise in alkaline phosphatase. The failure to demonstrate hypercalcuria conclusively by the Sulkowitch test was in all probability due to polyuria and resulting dilution. It is unfortunate that no determination of twenty-four-hour urine calcium excretion is available to support this hypothesis.

The terminal clinical course was typically manifested by increasing uremia, reversal of the calcium-phosphorus ratio, fixation of the urine specific gravity at 1.010, coma and death. The many months of high serum phosphorus led to metastatic calcification in the kidneys, heart, lungs and stomach and practically all the arteries examined. The arteriosclerosis and chronic renal disease caused hypertension, myocardial hypertrophy and terminal coronary thrombosis. The possibility of terminal "parathyroid poisoning" in this patient should be considered, particularly since cardiovascular complications have been observed in previously reported cases.[4] However, Albright and Reifenstein[4] state

Figure 4. *Photomicrograph of the Surgical Specimen of Parathyroid Gland, with Atrophy of Cell Cords and Increase in Connective Tissue (Hematoxylin and Eosin Stain X75).*

that the critical level of serum calcium is about 17 mg. per 100 cc.; the terminal level in the patient described above was only 10.3 mg. per 100 cc.

The apparently increased incidence of peptic ulcer in hyperparathyroidism is interesting. Albright and Kerr[5] reported 4 peptic ulcers in 28 cases of primary hyperparathyroidism. Three other patients had symptoms of the upper digestive tract. This association has been observed in other series as well.[6] Worthy of note, however, is the fact that hypercalcemia per se may cause anorexia, nausea, vomiting, epigastric pain and marked constipation. This patient had all, particularly the last. We did not demonstrate an ulcer, but believe that the duodenal diverticulum or gastrojejunostomy, or both, may have been ulcerated at one time.

Summary

A case fulfilling most of the requirements of the Burnett syndrome is presented. The basic pathological change was found to be a parathyroid adenoma. It is suggested that the Burnett syndrome may represent primary hyperparathyroidism associated with an excessive intake of absorbable alkali and resulting atypical chemical changes.

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THROMBOCYTHEMIA*

Report of Three Cases and Review of Literature

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IN the past study of the myeloproliferative disorders of the bone marrow has been devoted to the red-cell and white-cell series. To be sure, some attention has been paid to the relation of the megakaryocytes to thrombocytopenia, but, strangely enough, there have been few observations of excessively high platelet counts and megakaryocytic hyperplasia. Tocantins[1] has described moderate increases in the platelet count from various stimuli — for example, fractures, operations, hypochromic anemia and dermatoses. This increase is called thrombocytosis and is probably not uncommon. Little is known about the histology of the bone marrow in such conditions.

In contrast there is a rare condition, thrombocythemia, in which the platelet count is permanently elevated to more than three times the normal value. In addition there is hyperplasia of the megakaryocytes in the bone marrow, a tendency for venous thrombosis and spontaneous hemorrhage. Various names have been applied to this condition, such as thrombocythemia, thromboblasthemia, piastrinemia and hemorrhagic thrombocythemia.[2, 3]

Case Reports

CASE 1. M. F., a 63-year-old woman, had been hospitalized in 1947 because of abdominal pain. Examination revealed a duodenal ulcer and gastric stasis. Hematologic survey disclosed a red-cell count of 5,000,000, with a hemoglobin of 15 gm. per 100 cc., and a white-cell count of 17,400, with 88 per cent neutrophils. Tests of liver and renal function were within normal limits. A subtotal gastrectomy was performed. The spleen was also removed because it was enlarged. The microscopical diagnosis was fibrosis of the duodenum compatible with a healing ulcer and congestion of the spleen. The immediate postoperative course was uneventful.

A few weeks later the patient was admitted to the Rhode Island Hospital because of hyperemesis due to intestinal obstruction. After a lysis of adhesions and a jejunojejunostomy there was a steady improvement and she was soon discharged. The hemoglobin was 11 gm. per 100 cc., the white-cell count 17,000, and the hematocrit 45 mm. with a buffy layer of 5 mm.

She was readmitted to the hospital 3 years later because of recurrent epistaxis, increased weakness and fatigue. Physical examination revealed no significant abnormality.

Examination of the blood showed a red-cell count of 3,390,000, with a reticulocyte count of 1.1 per cent and a hemoglobin of 9.2 gm. per 100 cc., and a white-cell count of 17,500, with a normal differential. The direct platelet count ranged between 3,800,000 and 4,400,000 per cubic millimeter (normal, 150,000 to 300,000 per cubic millimeter). Blood indexes and red-cell fragility tests were within normal limits. The hematocrit was 20 per cent, but the buffy layer was 10 mm. in the hematocrit tube. The bleeding time was 6 to 13½ minutes (normal, 1 to 3 minutes by the Duke technic). The clotting time was 6½ to 7½ minutes (normal, 5 to 10 minutes by the Lee-White method). Clot retraction was complete in less than 18 hours. There was no evidence of fibrinolysin. Prothrombin activity of plasma (Quick method) was 70 per cent of normal. All other blood chemical constituents were normal. The Rumpel-Leede test was negative, as was the test for cold agglutinins. Bone-marrow biopsy revealed megakaryocytic hyperplasia as well as erythropoietic hyperplasia without maturation arrest. Another biopsy subsequently taken was histologically similar.

X-ray examination of the chest, gastrointestinal tract and kidneys was negative. The patient was placed on liver extract, and the reticulocyte count rose to approximately 14 per cent. She was given 1500 cc. of fresh whole blood, and iron therapy begun. Her response was adequate, with a hemoglobin of 11.5 gm. per 100 cc. and a red-cell count of 4,120,000; the white-cell count remained elevated at 22,600, and the platelet count was 4,860,000. She was afebrile and asymptomatic and was accordingly discharged.

On this regimen the patient did well for approximately 2 years until her death, which was thought to be due to bronchopneumonia. No autopsy was performed. The platelet count at all times remained elevated, ranging between 1,350,000 and 5,200,000.

This patient had had a subtotal gastrectomy for a duodenal ulcer and a splenectomy because of splenic enlargement. Subsequently, a greatly elevated platelet count developed. The thrombocythemia is considered to have been secondary to the splenectomy.

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Case 2. M. P., a 37-year-old deck officer, was first studied in 1948, when a routine blood smear revealed a "great increase in platelets." He gave a history of headaches and easy bruising, with resultant ecchymoses. He was otherwise asymptomatic and in apparently good health.

Physical examination showed the heart to be slightly enlarged. Splenomegaly was demonstrated on x-ray examination but not by palpation.

Initial examination of the blood demonstrated a red-cell count of 3,960,000 and a white-cell count of 7600, with a normal differential. Clot retraction and blood indexes were normal. The platelet count was 12,000,000. The coagulation time in glass and silicone was normal (Quick method). The bleeding time ranged between 6 and 9 minutes. Tests of renal and liver function were normal. Bone-marrow biopsy revealed massive megakaryocytic hyperplasia, without hyperplasia of other elements.

The patient was released to full duty and was instructed to return to the hospital every year for follow-up study. The results of the laboratory examinations during 4 successive years are presented in Table 1.

Table 1. *Results of Laboratory Examinations in Case 2.*

Year	Red-Cell Count	White-Cell Count	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Platelets	Bone-Marrow Findings	Clot Retraction	Bleeding Time
	x 10^6	x 10^3	%	%	%	%	x 10^3			min.
1949.....	3.7	9.3	71	27	1	1	14.03	Megakaryocytic hyperplasia	Excellent	6
1950.....	4.2	22.1	84	13	1	2	11.72	Megakaryocytic hyperplasia	Excellent	15
1951.....	3.9	9.2	66	30	2	2	13.60	—*	Excellent	7
1952.....	4.1	6.3	54	37	4	5	10.80	—*	Excellent	6

*Patient refused to submit to bone-marrow biopsy.

In the course of a routine physical checkup in this case thrombocythemia was demonstrated. The patient bruised easily and had a prolonged bleeding time. Bone-marrow biopsy revealed megakaryocytic hyperplasia. There was x-ray evidence of an enlarged spleen. The patient has been followed for five years with the same findings except that on one occasion a leukocytosis was demonstrated. Because we do not know the cause of the splenomegaly, the possibility of a thrombocythemia secondary to an intrinsic disease in the spleen has not been ruled out. It is classified as idiopathic thrombocythemia because the patient has been followed for a considerable time without the demonstration of any other disease. The splenomegaly is minimal, being apparent only on x-ray examination.

Case 3. O. McC., a 67-year-old man, was hospitalized because of symptoms of intermittent claudication ascribed to arteriosclerosis obliterans of the extremities, with superimposed thrombosis.

Physical examination showed the heart to be enlarged and the peripheral pulses of the lower extremities absent. The right great toe was cool, swollen, tender and blue. The spleen was not palpable.

Examination of the blood disclosed a red-cell count of 3,910,000 – 4,200,000, with a hemoglobin ranging between 9.5 and 12.3 gm. per 100 cc., and a white-cell count of 5200, with 59 per cent neutrophils, 40 per cent lymphocytes and 1 per cent eosinophils. The feces were guaiac negative. The hematocrit was 32 mm., with a 5-mm. buffy layer. The platelet count was 1,470,000. Prothrombin activity of plasma (Quick method) was 90 per cent of normal. Clot retraction, liver function and an electrocardiogram were within normal limits.

On the 2d hospital day the patient suddenly became incontinent of feces, began to have diarrhea and voided frequently and a high fever developed. He became drowsy, semicomatose and hypotensive. Several ecchymotic areas developed on the skin. In spite of hydration, blood transfusions, antibiotics and other supportive measures he died that evening.

At autopsy, which was limited to the chest and abdomen, the significant findings were in the adrenal glands and bone marrow. There was microscopical evidence of venous thrombosis, with hemorrhagic infarction of the right adrenal gland. The bone marrow showed greatly increased numbers of megakaryocytes and megakaryoblasts in varying stages of maturation. The left adrenal gland was atrophied.

The autopsy gave no evidence of leukemia or other diseases to which a secondary platelet elevation might be ascribed. The infarction of the adrenal gland was due to venous thrombosis, possibly secondary to the thrombocythemia. It is emphasized that the elevated platelet count (1,470,000) was observed before the acute episode on the second hospital day. The death of this patient is believed to have been due to acute adrenal insufficiency. The sudden onset and consequent short follow-up study make evaluation difficult. This is best considered as a case of idiopathic thrombocythemia.

Discussion

Most of the authors reporting cases of thrombocythemia have attempted to differentiate primary and secondary thrombocythemia. It is recommended that the term "idiopathic" be used in preference to "primary" for cases of unknown etiology and not associated with a major pathologic process. The cases of thrombocythemia occurring in association with a major disease, with a splenic lesion or after splenectomy are classified as secondary thrombocythemia.

A review of the cases of thrombocythemia reported in the literature demonstrates some significant laboratory findings (Table 2). Evaluation of some of these 28 cases, including the 3 reported above, is difficult because of the lack of essential histologic examination. Nineteen are classified as secondary, 6 as probably secondary, 1 as possibly idiopathic and 2 as idiopathic.

In 8 of the secondary cases the basic pathologic process was myelogenous leukemia. Six cases were associated with some phase of polycythemia vera, and 2 with carcinoma. In 1 case there was Boeck sarcoid, and 1 case was associated with hyperadrenalism. Two cases were associated with splenic atrophy or splenectomy.

The association of increased numbers of platelets with myelogenous leukemia or polycythemia vera is well known.[24] However, a platelet count of 1,000,000 is unusual. We believe that this excessive increase is an additional manifestation of a myeloproliferative disease rather than an independent phenomenon. For this reason these cases are listed as secondary thrombocythemia.

The relation between carcinoma and thrombocythemia is an interesting one. It is known that necrosis stimulates platelet formation, and, since there is usually necrosis in a tumor, this may possibly be a factor in the production of thrombocythemia. It is analogous to the leukemoid reactions that occur with tumors.

In the case associated with hyperadrenalism, this platelet elevation may be due to megakaryocytic hyperplasia stimulated by excessive hormone secretion by the adrenal cortex. This is conjectural since cortisone does not cause a platelet-count elevation in people free of disease.

Leitner[17] has suggested that in his case of thrombocythemia associated with Boeck sarcoid there may have been involvement of the spleen by sarcoid, with consequent release of the bone marrow from the hormonal inhibitory effect of the spleen. The occurrence of thrombocythemia in splenic atrophy or after splenectomy is possibly due to a similar mechanism. Lachnit's[20] case of thrombocythemia in the presence of a splenic-vein thrombosis

TABLE 2. *Laboratory Data in 28 Cases of Thrombocythemia.*

AUTHOR	AGE	SEX	RED-CELL COUNT	WHITE-CELL COUNT	PLATELETS
	yr.		x 10^6	x 10^3	x 10^3
Dubinskaja[4] (1928) — Case 1	46	M	3.7	21	(Increased)
Dubinskaja[4] (1928) — Case 2	48	F	4.3	23	(Increased)
Akazaki & Hamaguchi[5] (1939)	40	F	1.3–4.8	3–15	0.02–2.8
Mortensen[8] (1948)	69	M	2.7–9.8	21–54	1.5–6.0
Revol[9] (1950)	60	F	1.9–4.5	15–22	0.3–1.0
Boros & Korényi[7] (1931)	24	F	2.8	187	0.37
Di Guglielmo[6] (1920)	47	F	7.5	20	(Increased)
Drake[9] (1936)	65	F	4.5–5.8	20–30	1.0–2.6
Epstein et al.[10, 11] (1934)	56	M	3.0–7.5	13–20	1.2–2.2
Uotila[12] (1938)	62	M	3.8–7.3	14–43	1.0–5.0
Rowlands & Vaizey[13] (1938) — Case 2	40	F	5.5–7.1	8–18	0.5–1.8
Söderström[14] (1946)	63	M	4.9–5.6	12–23	1.2–2.2
Lebel[15] (1947)	57	M	5.6–7.0	32–44	0.4–1.2
Holst[16] (1948)	45	M	3.6–5.9	19–31	0.6–0.9
Leitner[17] (1945) — Case 1	45	M	3.9	6.6	0.76
Spangberg & Zettergren[18] (1949)	45	F	2.7–4.1	8–70	0.2–5.2
Leitner[17] (1945) — Case 2	26	M	3.2–4.3	52	0.23–9.87
Leitner[17] (1945) — Case 3	43	F	4.6–5.3	6.8–10	0.54–0.68
Present series (1953) — Case 1	63	F	3.4–5.0	14.8–22.6	1.5–5.2
Rowlands & Vaizey[13] (1938) — Case 1	59	M	2.8–4.7	5–18	0.32–1.9
Reid[19] (1940)	71	F	4.8–5.5	14–18	1.7–3.8
Lachnit[20] (1940)	46	F	2.8–5.0	14–20	0.5–1.0
Owren[21] (1943)	49	F	4.4–4.9	8–13	1.2–1.4
Jasinski[22] (1949)	68	F	3.1–4.2	6.4–27.7	0.5–1.8
Hemmeler[23] (1948)	29	F	4.1	0.3–12	0.25–3.3
Revol[9] (1950) — Case 2	41	M	0.5–4.0	4.8–80	0.7–4.1
Present series — Case 2	37	M	3.7–4.3	6.3–22	10.8–14
Present series — Case 3	67	M	3.9–4.2	4.9–5.2	1.4–1.5

TABLE 3. *Differential Diagnosis of Idiopathic Thrombocythemia, Myelogenous Leukemia and Polycythemia Vera.*

DISEASE	PLATELET COUNT	ANEMIA	WHITE-CELL COUNT	CHARACTERISTICS OF DIFFERENTIAL COUNT	LIVER	SPLEEN	INFILTRATION OF ORGANS
Thrombocythemia	Marked elevation*	May be present	Occasionally elevated	Inconstant granulocytosis with immaturity	No enlargement	Inconstant enlargement	Absent
Myelogenous leukemia	Moderate elevation	Present	Extremely high	Marked granulocytosis with immaturity	Enlargement present	Marked enlargement	Present
Polycythemia vera	Moderate elevation	Absent	Moderately high	Moderate granulocytosis	Inconstant enlargement	Enlargement usually present	Absent

*Three times normal value.

and subsequent splenectomy fits into the same classification.

Although in the cases reviewed there are no examples of thrombocythemia secondary to Hodgkin's disease, it has been stated that platelet elevation may occur.

Based on these cases of secondary thrombocythemia a schema is suggested that may have some bearing on the pathogenesis of the platelet elevation. Secondary thrombocythemia may be due to a myeloproliferative stimulus (myelogenous leukemia, polycythemia vera, carcinoma) or to the removal of a hormonal inhibitory effect on the megakaryocytes of the bone marrow (splenectomy, splenic atrophy, replacement of splenic function by disease).

The actual existence of idiopathic thrombocythemia as a pathologic entity is open to question. One can make such a diagnosis only by ruling out an underlying, basic disease. Unfortunately, it is not always possible to obtain essential biopsy or autopsy. The finding of an enlarged liver and spleen suggests secondary thrombocythemia, which can only be ruled out by adequate histologic examination of these organs. It is our impression that cases of idiopathic thrombocythemia exist — for example, Cases 2 and 3 reported above. However, only as more cases are reported can such a concept be proved.

Thrombocythemia appears to be a manifestation of a proliferative disorder of the bone marrow, inti-

TABLE 2 (*Concluded*).

Hemorrhagic Diathesis	Tendency to Thrombosis	Splenic Enlargement	Megakaryocytic Hyperplasia	Type of Thrombocythemia	Basic Pathologic Process
+	+	+	+	Secondary	Myelogenous leukemia
−	−	+	+	Secondary	Myelogenous leukemia
+	−	+	+	Secondary	Myelogenous leukemia
+	−	+	+	Secondary	Myelogenous leukemia
+	−	+	+	Secondary	Myelogenous leukemia
+	?	+	+	Secondary	Acute leukemia
+	?	+	+	Secondary	Myelogenous leukemia in transition from polycythemia vera
+	−	+	+	Secondary	Myelogenous leukemia in transition from polycythemia vera
+	+	−	+	Secondary	Polycythemia vera "exhausted"; splenic atrophy.
+	+	+	+	Secondary	Polycythemia vera
+	+	+	+	Secondary	Polycythemia vera
+	−	+	+	Secondary	Polycythemia vera
+	+	+	+	Secondary	Polycythemia vera
+	+	+	+	Secondary	Polycythemia vera
−	−	−	+	Secondary	Bronchogenic carcinoma
+	+	+	+	Secondary	Carcinoma of stomach; cirrhosis of liver.
−	−	+	+	Secondary	Boeck sarcoid
−	−	−	+	Secondary	Hyperadrenalism
+	−	+	+	Secondary	Splenectomy
+	−	−	?	Probably secondary	(No bone-marrow biopsy)
+	+	+	+	Probably secondary	Hepatosplenomegaly (without biopsy)
+	+	+	+	Probably secondary	Platelet elevation before splenectomy
−	−	+	+	Probably secondary	Hepatosplenomegaly (without biopsy)
−	−	+	+	Possibly idiopathic	Hemolytic anemia
+	+	+	+	Probably secondary	(No biopsy of spleen)
+	+	+	+	Probably secondary	Hepatosplenomegaly; inconstant platelet elevation.
+	+	+	+	Idiopathic	Splenomegaly (x-ray study — no biopsy)
+	+	−	+	Idiopathic	—

TABLE 3 (*Concluded*).

Disease	Bleeding Time	Venous Thrombosis	Spontaneous Hemorrhage	Coagulation Time	Bone-Marrow Hyperplasia		
					Megakaryocytic	Erythrocytic	Leukocytic
Thrombocythemia	Prolonged	Frequent	Frequent	Normal	Invariably present	Sometimes present	Absent
Myelogenous leukemia	Occasionally prolonged	Rare	Rare	Sometimes prolonged	Rarely present	Rarely present	Invariably present (in extreme degree)
Polycythemia vera	Normal	Rare	Rare	Normal	Sometimes present	Invariably present (in extreme degree)	Invariably present (in moderate degree)

mately connected with the other proliferative diseases of this tissue. Although we have not seen any cases of so-called primary thrombocythemia that were transformed into myelogenous leukemia, the frequency of association suggests the possibility. On the other hand some cases of thrombocythemia may initially have been polycythemia vera. The case described by Epstein and Goedel[10] is an example, although in this case there was splenic atrophy, which was probably a more important fact. We have considered Case 1 reported above as a possibility, since the red-cell count was 5,000,000 on the first determination and may previously have reached polycythemic levels. It is more probable that splenectomy initiated the thrombocythemia since it occurred after this operation.

Table 3 lists the differential points between thrombocythemia, myelogenous leukemia and polycythemia vera.

We do not believe that idiopathic thrombocythemia is a form of megakaryocytic leukemia. The tissues of the body are not infiltrated by platelets, megakaryocytes or megakaryoblasts, nor is there any significant extramedullary platelet formation. The bone marrow contains increased numbers of megakaryocytes and megakaryoblasts, but there is no complete replacement of the bone marrow by these cells.

There is a group of diseases called myeloid megakaryocytic hepatosplenomegaly,[25] chronic nonleukemic myelosis,[26] acute megakaryoblastic leukemia, erythroleukopiastrinemia and hyperthrombocytic myelosis.[27] The patients usually have an increased platelet count, with large, bizarre platelets intermingled with megakaryocytes and granulocytes in varying stages of maturation. There is hepatosplenomegaly, with extramedullary hematopoiesis. The bone marrow does not consistently show myeloid hyperplasia of the degree usually seen in myelogenous leukemia. These cases are poorly understood and are considered by some to be atypical myelogenous leukemia. The cases reported by Di Guglielmo,[5] Dubinskaja,[4] and Boros and Korényi[7] are of this type. The findings of hepatosplenomegaly with extramedullary hematopoiesis and myeloid hyperplasia of the bone marrow strongly resemble those in the more obvious cases of myelogenous leukemia.

Idiopathic and secondary thrombocythemia is chiefly a disease of adults, occurring equally in both sexes. The patients complain of easy fatigability and weakness. There is a tendency to venous thrombosis and to spontaneous hemorrhage. The bleeding time may be prolonged. In addition to the abnormal hematologic findings already described it should be noted that anemia may be present although inconstantly so. The red cells may show Howell–Jolly bodies and stippling. There is a tendency to leukocytosis, with occasional eosinophilia.

It is possible that the increased number of platelets make the blood more viscid and thus favor clot formation. This may be the explanation for the high incidence of venous thrombosis. It is reminiscent of the thrombotic tendencies in polycythemia vera.

The cause of the spontaneous hemorrhages and prolonged bleeding time is not known.

A description of the pathology of idiopathic thrombocythemia can be given only on the basis of information derived from the limited number of possible cases of idiopathic thrombocythemia. The bone marrow contains increased numbers of megakaryocytes and megakaryoblasts. Occasionally, there are clumps of agglutinated platelets. Hyperplasia of the other blood cells in the bone marrow may occur, but this is more commonly seen in thrombocythemia secondary to polycythemia vera or myelogenous leukemia.

The elevated platelet count has been repeatedly mentioned. The platelets vary in size, sometimes reaching giant proportions, up to about a third the size of a red blood cell. These enlarged platelets show increased prominence of granular centers. Multinucleated giant cells resembling megakaryocytes are occasionally seen.

Although splenomegaly has frequently been noted the number of pathological examinations of this organ is insufficient for a satisfactory description. The splenomegaly associated with secondary thrombocythemia is usually due to involvement by the major disease.

Summary

Three cases of thrombocythemia are reported. One occurred after splenectomy, and the other 2 were idiopathic.

The literature of thrombocythemia is reviewed, and the significant findings discussed. The cases are classified as idiopathic or secondary thrombocythemia. The existence of idiopathic thrombocythemia as a pathologic entity needs further proof. The cases of secondary thrombocythemia occurred in association with myelogenous leukemia, polycythemia vera, cancer, splenic disease or after splenectomy.

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EFFECTS OF PENTYLENETRAZOL ON SENILE PATIENTS

A Clinical Study

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AT the Long Island Hospital in Boston the patients are mainly chronically ill elderly people, many of whom suffer from cardiovascular disease and have a history of cerebral hemorrhage. Often, they are depressed, disorientated and confused. Thus they should be suitable subjects for analeptic therapy since they correspond in type to the patients in whom Chesrow et al.,[1] Fong,[2] Smigel and his associates,[3] Seidel, Silver and Nagel,[4] Jensen and Leiser[5] and others have reported good results with oral administration of pentylenetrazol (Metrazol). Smigel and his co-workers also cited improved appetite, red-cell count and hemoglobin after the same form of treatment.

Most investigators found that even when mental confusion was not alleviated by the therapy the patients frequently became more amenable to ward care and less resistive or destructive. With the chronic shortage of nursing personnel this alone is a significant achievement.

In addition to a general tonic effect it was found that pentylenetrazol, instead of increasing hypertension, often lowered the blood pressure.[1,3] A review of the literature also showed that the level of blood pressure increased only in cases of hypotension. Thus, Haury and Gruber[6] saw no vasoconstriction but found that the drug dilated both splanchnic and cerebral vessels. Forbes and Nason[7] reported dilatation of the blood vessels of the brain, and Messinger and Moros[8] saw no pronounced changes in blood pressure even with convulsive doses.

It was therefore decided to evaluate this drug as an analeptic in senile states, with particular attention to the question whether it increased cerebral blood flow and raised the blood pressure, increasing the tendency to intracranial bleeding. Above all, it was desired to determine the innocuousness of this therapy for hypertensive patients.

For the study a group of 10 men and 10 women were selected, and in general the therapeutic regimen laid down by the authors cited above was followed.

The average age of these patients was over seventy. It varied from sixty-three to eighty-six years. Although the blood-pressure readings averaged only 164 systolic, 95 diastolic, some of the patients had a systolic pressure of 190 or more and a diastolic pressure of 110. A number, both men and women, had had cerebral hemorrhages with more or less prominent residual symptoms. All showed slowing of the mental processes and were rather apathetic, but none were actually psychotic. All were at least partially bed ridden — some completely so.

The lesions presented in these cases were quite similar and could be classified as arteriosclerotic heart disease, myocardial insufficiency, general or cerebral arteriosclerosis, or both, hypertension and status post hemiplegia.

A number of patients suffered from arthritis. The laboratory studies showed moderate albuminuria and anemia in some cases, but were otherwise not significant.

To test the effect of dosage 5 men and 5 women were put on 1 tablet (0.09 gm.) of pentylenetrazol four times a day, and the other 10 patients received 2 tablets four times a day. This medication was continued for two months. In most cases in which improvement occurred it usually became noticeable in seven to ten days. Table 1 gives the results achieved after two months of treatment.

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The result was considered excellent when a dull, moody or despondent, irritable, confused and complaining patient became bright, pleasant, oriented and co-operative; in other words a definite improvement in the state of well-being became evident. Frequently, improvement in appetite went hand in hand with this change for the better. Also, a patient who was almost completely bed ridden would spontaneously get up for meals or to go to the bathroom. Lesser degrees of improvement were along the lines described but less prominent. Thus, a fair result might be represented by lessened torpidity or by quicker response to questions or commands. Some patients showed improvement in sleep pattern as described in previous reports, but blood cytologic, chemical and urinary findings, as well as basal metabolic rates, showed no significant changes. In no case did blood pressure, either systolic or diastolic, rise.

TABLE 1. *Results of Oral Administration of Pentylenetrazol.*

CASE No.	SEX	AGE	RESULT
		yr.	
One tablet 4 times daily:			
1	F	70	Good (marked improvement)
2	F	73	Fair (moderate improvement)
3	F	66	Excellent (remarkable improvement)
4	F	68	Poor (no improvement)
5	F	66	Fair (moderate improvement)
6	M	65	Fair (moderate improvement)
7	M	80	Poor (no improvement)
8	M	63	Excellent (remarkable improvement)
9	M	86	Poor (no improvement)
10	M	80	Poor (no improvement)
Two tablets 4 times daily:			
11	F	77	Good (marked improvement)
12	F	69	Fair (moderate improvement)
13	F	66	Fair (moderate improvement)
14	F	68	Excellent (remarkable improvement)
15	F	77	Excellent (remarkable improvement)
16	M	72	Excellent (remarkable improvement)
17	M	65	Poor (no improvement)
18	M	76	Excellent (remarkable improvement)
19	M	74	Excellent (remarkable improvement)
20	M	65	Good (marked improvement)

Although the cases studied are too few to give statistical significance to the results, it is suggestive that with two tablets four times a day a much larger percentage of improvement was seen than with one tablet four times a day: excellent results in 5 cases, good in 2, fair in 2 and failure in 1, as against excellent in 2, good in 1, fair in 3 and failure in 4. The significance of this difference in the results of the two groups is increased by the fact that two tablets four times a day represented the usual dosage recommended as effective by most authors.

CASE REPORTS

The following cases illustrate what we considered to be an excellent result.

CASE 16. A. B., a 72-year-old man, was first admitted to the hospital in 1932 at the age of 51 with cardiac insufficiency. He was readmitted in 1950 on the day after a cerebral accident. Speech was impaired, and there was weakness of the left arm and leg. The blood pressure was 194/110, and the pulse 110. The heart was enlarged, with rales at both lung bases. Left-sided reflexes were hyperactive, and Babinski reflexes were present; facial muscles on the left were weak. The patient improved under digitalis but became despondent, irritable and confused. The diagnoses were hypertensive heart disease and hemiplegia (mild) on the left.

The patient was placed on pentylenetrazol for 2 months — 2 tablets 4 times daily. (Before the medication was given his blood pressure was 168/104, with a pulse rate of 90.) The urine was normal, and the blood Hinton test was negative. The blood sugar was 100 mg., and the nonprotein nitrogen 24 mg. per 100 cc.

After 1 week's medication the patient became more cheerful and bright; there was definite improvement in his general well-being and reaction time, and he became more ambulatory. After 2 months of medication, the blood pressure was 164/102, and the pulse rate 84. No change in the weakness of the left side of the body was noted. About 2 weeks after the medication had been discontinued he reverted gradually to practically his former status as far as his mental attitude and behavior were concerned.

CASE 15. L. B., a 77-year-old woman, was quite deaf. She was oriented regarding place and person but vague about time — not knowing the day of the week or the month of the year. Her memory for past events was noticeably impaired. She was ambulatory. Her intelligence was apparently dulled by senile retardation. At times she was quite unco-operative. She complained of poor appetite and weakness.

Examination of the heart revealed a Grade 2 systolic murmur at the apex. The blood pressure was 140/82, and the pulse 86. Examination of the lungs was negative. The urine and blood were normal, and the blood Hinton test was negative. The blood sugar was 90 mg., and the nonprotein nitrogen 30 mg. per 100 cc. The diagnosis was generalized arteriosclerosis.

The patient was given 2 tablets of pentylenetrazol 4 times daily for 2 months. After 10 days her appetite improved, and she became much more co-operative and cheerful. Her memory also showed improvement. After 2 months the blood pressure was 140/80. Two weeks after the medication had been discontinued she reverted to her former status.

DISCUSSION

It is to be stressed that even with the higher dosage of 8 tablets a day no side effects or complications and no increase in blood pressure occurred. Even in Case 16 the blood pressure showed no tendency to rise to its former level but remained the same when the patient was put on pentylenetrazol, whereas the pulse rate decreased somewhat. Although no effect on the blood picture was demonstrable as a result of the therapy all but 5 of the 20 patients gave some signs of physical and mental improvement such as greater and quicker responsiveness, less depression or confusion and a better physical status.

To determine the duration of the tonic effect the medicament was withdrawn after two months. About two weeks later the patients began gradually to regress to their former status. It is evident that to ensure a more lasting effect the drug must be given over a longer period and that after maximum benefits have been achieved maintenance doses should be used as described in the literature.

SUMMARY

To study the effect of oral therapy with pentylenetrazol (Metrazol) 20 patients were selected and divided into two groups of 10 each, one group receiving one tablet of the drug four times a day and

the other two tablets four times a day. The group receiving the larger dosage showed a greater percentage and degree of improvement than the other.

This improvement was both mental and physical.

These results are in close accord with those previously reported in the literature. In no case did the therapy increase either normal or hypertensive blood levels.

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SPECIAL ARTICLE

MEDICINE AND THE LAW*

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Legal medicine is frequently defined as the application of medical knowledge to the needs of justice. However, the subject can be viewed more precisely by separation into two major divisions. The first involves a physician's practice of his special skills in medicolegal investigations, and the second a legal evaluation of the physician's personal, ethical and professional conduct.

The Physician in Medicolegal Investigations

The first subdivision involves situations in which a physician acts objectively in applying special skills to the study of matter submitted and afterward reports on it or testifies to it. These situations include the practice of forensic pathology, toxicology and hematology.

The importance of improving such medicolegal investigation becomes apparent when it is realized that about 20 per cent of all deaths in the United States result from violence or occur unexpectedly from obscure causes; that each year approximately 1 murder for every 10,000 living persons is officially recognized; and that since, in many localities, the investigation of violent or obscure deaths is insufficient, the number of murders that actually takes place or the number of deaths from accident, suicide or natural causes that is erroneously attributed to murder cannot be estimated. Once these facts are understood the vital importance of more numerous and better qualified medicolegal investigators becomes apparent.

Legal Aspects of Medical Practice

The more important phase of legal medicine is, however, the second subdivision — the phase in which a physician is personally involved by being brought into a case either as an expert witness or as a defendant through an allegation that he has infringed the law in some respect and has thus become subject to criminal or civil action or to citation before a board of medical examiners, for if a patient sues the physician and proves by a preponderance of all the evidence that he suffered injury because the physician failed to act in accordance with the standard of practice in the community, the patient may recover a judgment for money damages.[1] It is in this area that members of the medical profession need a more comprehensive educational program. This paper can, of course, do no more than indicate the most vital areas in which the physician must be informed.

If a physician is to escape legal liability and penalty it is obviously essential that he have some understanding not only of his legal obligation to his patient but also of statutes and court decisions that are directly related to or have application to circumstances associated with the physician-patient relation. This point is most obvious in cases involving such matters as adoption, abortion, artificial insemination, sterilization, workmen's compensation and narcotics.

In most jurisdictions the newly licensed physician must present his license for registration with the county clerk and, usually, with the local representative of the health department. Furthermore, before he may dispense or prescribe narcotics, he must register with the Bureau of Narcotics of the Internal Revenue Service. In many jurisdictions it is required that a special prescription pad, obtainable from the state narcotic agency, be used in prescriptions for narcotic drugs. A copy of the local state narcotic act may be obtained from the designated state agency. Information concerning federal nar-

*Adapted from the chapter of the same title in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publishers, Little, Brown and Company, Boston.

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cotic regulation may be obtained from the local district supervisor, United States Bureau of Narcotics.

The health department supplies various forms, together with essential pertinent information that will permit the young physician to know and comply with the law respecting the reporting of births, deaths, communicable diseases and so forth. In many states the law requires the physician to report cases of violent or criminal injury to the chief of police (or to the sheriff). Such reports are not generally required for accidental injury unless the patient dies.

In all jurisdictions registration statutes require that a report of birth, stillbirth or death of an infant be filed with a designated agency. In such statutes live birth is generally defined as one in which there is evidence of life after the child is completely outside the mother. Stillbirth has reference to a fetus that gives no evidence of life after complete birth, provided uterogestation has advanced through five months, twenty weeks or more.

In the event of a live birth followed by death the filing of both a birth and a death certificate is necessary. In stillbirths the filing of a special stillbirth certificate is required in many states (Alabama, California, Connecticut, Florida, Idaho, Illinois, Indiana, Iowa, Louisiana, Maryland, Nevada, Ohio, Oregon, South Carolina, Utah, Virginia, Wisconsin and Wyoming); under statutes of other states a stillbirth requires the filing of both a birth and a death certificate (Arizona, Colorado, Delaware, Georgia, Kentucky, Michigan, Missouri, Nebraska, New Jersey, New York, North Dakota, Pennsylvania, Rhode Island, Texas, Vermont, Washington and West Virginia).

It should be particularly borne in mind that each state has its own statutes forbidding an attending physician to sign a death certificate in certain cases. These cases generally include any violent or suspect death, whether homicidal, suicidal or accidental; any death in which the physician has not been in attendance; any death in which the physician is unable to establish the cause of death with reasonable clinical probability; and any death in which it appears that a criminal act may have been a contributing cause. All cases coming within the provisions of the statute must be referred to the designated authority, usually the coroner or the medical examiner.

The physician entering practice needs to inform himself of the provisions of the workmen's compensation act in his state. These differ so much in detail in the several jurisdictions that generalization concerning them is not profitable.

A physician is not likely to practice long in a given locality before it becomes necessary for him to appear in court as an expert witness. Expert witnesses are those who are skilled in any science, art, trade or occupation. The ordinary witness must, with few exceptions, testify to facts within his own knowledge. In contradistinction, the expert witness is called upon to give opinion evidence. The medical expert witness is used in a great variety of cases, including criminal trials, insanity and probate contests, cases arising under life, health and accident policies and actions because of personal injury.

It is probable that juries are more likely to distrust the testimony of the medical expert than that of any other witness; when a physician, in court or before an industrial-accident commission, presents himself successively as an expert in eight or ten fields of specialty practice, it is not unreasonable to doubt his qualifications or his integrity. This being true, the content of a medical expert witness's opinion may be only a little more important than the manner in which he delivers it — that is, than the impression he makes on the jury.

The expert should be professional in manner, using language understandable to the lay jury. He should be earnest and sincere, and avoid the appearance of being an advocate for any party. It is his function and privilege to contribute to the end that truth and justice may prevail.

No reasonable person will argue with the theory of law providing that a person who has been injured by the carelessness or ignorance of another person should be compensated for that injury; the fact that the injury has been caused by a physician affords no ground for varying from the rule.

There are meritorious malpractice claims — cases in which patients suffer injury as a result of the ignorance or negligence of physicians. The honest physician need have no fear of such a suit. He can avoid being justly charged with malpractice by caring for every patient with scrupulous attention to the requirements of good practice.

On the other hand the majority of all malpractice claims and suits that are brought against physicians are nonmeritorious — that is, they have no just foundation. Such claims are injurious to the profession and to the public alike.

Any patient may bring a malpractice action against any physician who has attended him professionally, although the Statute of Limitations provides a time after which specified actions are barred and may not be brought. The bringing of such an action does not, of course, suggest that the claim has any merit. Nevertheless, the practitioner who is the target of the accusation is damaged by the mere filing of the action.

When a patient alleges that he has suffered an injury because his medical attendant failed to care for him in accordance with the standards of skill, care, judgment and diligence that are commonly possessed and exercised by the ordinary, reputable practitioner in the community, the physician is being accused of professional negligence: he is

charged with malpractice. Otherwise expressed, professional negligence or malpractice consists in the physician's doing something he should not do or in omitting to do something that he should do in the professional care of his patient. The criterion for the evaluation of such an action is what the average physician in the community, in the same field of practice, would or would not do in similar circumstances.

If physicians were always able to obtain perfect results there would, of course, be no malpractice actions. But deaths, untoward and unexpected results, continuing disabilities and complications will continue to occur. Whether or not the patient brings an action is often determined by his feeling toward his physician. A patient who has a friendly feeling for the physician and who believes that everything possible has been done for him is not likely to sue for malpractice, even when the result is bad. Such suits are likely if the patient is resentful of some fancied or actual affront, if he believes that he has not been closely enough attended or, above all, if a third person raises a doubt in his mind regarding the propriety of the treatment.

A physician is not required to undertake the care of any patient, but once he assumes the responsibility he must give, or see to it that there is given, such care and treatment as the patient's condition makes necessary until he no longer needs attention or unless the physician is sooner discharged or withdraws from the case. Before a physician may withdraw from a case without legal liability, he must give reasonable notice of his intention and allow the patient reasonable opportunity to fill his place.

Many malpractice actions are brought as the result of some unwise statement made by the attending physician, or his partner, assistant or office nurse, to the patient or to a friend of the patient. Care should be taken to avoid making any remark constituting an "admission" of fault or one that may be construed as such. An admission on the part of the defendant may free the plaintiff from the necessity of offering medical expert testimony, which is required for proof of alleged negligence in the ordinary malpractice action.

The application of the doctrine of *res ipsa loquitur* in a case gives rise to an inference of negligence on the part of the defendant and relieves the plaintiff of the necessity of proving the alleged malpractice by the testimony of experts; it places on the defendant the burden of making explanation, if he can, to offset the inference of negligence. *Res ipsa loquitur* (literally, the thing speaks for itself) is a doctrine of the general law of negligence. It is held applicable whenever one person is injured by an instrumentality that is entirely in the control of another person and does not ordinarily result in injury if the person in control exercises due care.

The doctrine of *res ipsa loquitur* has been held applicable in the field of malpractice chiefly in cases that involve the slipping of instruments, foreign bodies left in the tissues, burns from heating modalities, irradiation injuries (generally limited to cases wherein the x-rays are being used diagnostically), infection through the use of an unsterilized needle or instrument and injury to a portion of an anesthetized patient's body outside the field of treatment or operation.

The precipitating cause of many malpractice actions is found in the unwise comments or criticism of physicians regarding treatment given to patients by other physicians. Commonly, it is criticism by a succeeding physician of the work of his predecessor on the case. Various authorities have estimated that 50 to 80 per cent of all the suits for malpractice would be eliminated if such destructive criticism could be stopped. It is profitless to attempt to determine why physicians are so likely to criticize destructively and unethically, but the results of it are deplorable. Legitimate criticism can rest only on full knowledge of the facts as gathered from the physician who treated the patient, as well as from the patient.

In the absence of evidence to the contrary it is legally presumed that a physician exercises the ordinary skill and care required of him in treating his patient. He is justified in his conduct of the case if it is such as would be approved by even a respectable minority of his associates in the same locality. A charge of malpractice is not warranted even by the fact that he made a mistake in diagnosis or was guilty of an error of judgment, that he might have employed other medicines or used other methods of treatment, that expert witnesses testify that they themselves would have employed a different method or that a bad result followed instead of a satisfactory one.

Experience has taught that the most careful attention to the dictates of good medical practice is not sufficient to ward off the unjust claim and that no physician is immune. The likelihood of being sued for malpractice must now be regarded as a definite occupational hazard for the practicing physician. *Caveat medicus!*

The physician-patient relation is one of trust and confidence. The physician is obligated to act at all times with the utmost good faith toward his patient. Thus, if he knows that he cannot accomplish a cure or that the treatment adopted will probably be of no benefit, it is his duty to advise his patient of the facts. It is extremely doubtful if a physician has a therapeutic privilege to withhold a specific diagnosis from a patient with serious or fatal illness. On the contrary it appears to be clear that, in ordinary circumstances, the confidential relation requires that the physician make a frank and full

disclosure when his patient is adult and mentally competent.

At common law confidential communications made by a patient to a physician were not privileged. In 31 American jurisdictions this situation has been changed by statute. In 22 states secrecy is required of the physician in criminal as well as in civil cases. The patient may waive the privilege by bringing certain actions as provided in the statutes, by implication through certain conduct on his part or by direct and specific waiver. Most of the statutes on privileged communication cover judicial proceedings only; the privilege of silence applies only to matters that are essential to treatment or to medical consultation.

In any event it is true, of course, that the *Principles of Ethics of the American Medical Association* require that confidences entrusted by the patient ordinarily must not be revealed and that the law of the right of privacy gives the patient additional protection. This is the right to be "left alone," or to live in seclusion without being subjected to unwarranted or undesired publicity. No medical case record should be published and no picture, still or motion, shown from which the identity of a patient is determinable, without his knowledge and authorization.

It is the personal concern of a physician for his patient that makes him different from a tradesman or a pure scientist. The art of the practice of medicine is of extreme importance to the patient, and its good exercise is protective to the physician.

A good physician-patient relation depends not only on the best possible medical service but also on maintaining of the patient's confidence and friendship. Skill is no substitute for warmth or kindness. However, a physician is unwise to tells his patient "not to worry about a thing." Physicians should not guarantee results of treatment; malpractice actions arise if failure occurs.[2]

The foregoing has touched on the major areas of legal medicine. To this discussion should be added at least a few of the more important precautions against malpractice.

Prevention of Malpractice Suits

It is fundamental that every patient must be cared for with close attention to the requirements of good medical practice. This comprehends sufficiency of investigation, observation and treatment and the utilization of every indicated laboratory aid. Thus "The failure to make use of x-ray as an aid to diagnosis in cases of fracture amounts to a failure to use that degree of care and diligence ordinarily used by physicians of good standing in the community and the court, in absence of expert testimony, may take judicial notice of such fact." (*Agnew* v. *City of Los Angeles* [Cal.], 218 Pac. (2d) 66.) It includes the protection of those coming in contact with the patient; the instruction of the patient and of those caring for him, so that all things needed may be carried out during the absence of the attending physician; and the recognition of the importance of psychologic factors so that the nervous, mental and emotional balance of the patient may be constructively influenced by tactful handling and the institution of proper psychotherapeutic measures.

It is also fundamental that, in undertaking the care of patients, the physician should accept only such cases as he is reasonably well qualified to handle. He must keep abreast of progress in his field of practice and should utilize only recognized and accepted procedures. In any case in which the patient is not doing well, in which there is any unexpected reaction or untoward occurrence or in which he or his family unduly complains or expresses dissatisfaction, a consultant should be brought in. The consultation affords great protection in the event that a claim of malpractice is later made. It is recommended that protective use of consultants be made routine, even in cases in which fees for consultation may not be available.

The physician must exercise care in delegating duties to assistants, nurses and technicians and in maintaining not only professional instruments and apparatus but also a safe environment in which to work. Instruments should be checked and apparatus calibrated as required in the exercise of ordinary care.

It must be recognized that it is hazardous to sterilize any patient in the absence of a medical indication; that it is dangerous to telephone a prescription, because of the possibility of error in transmission; and that it is unwise for a physician to testify, without taking legal advice, at a coroner's inquest in a case in which he has been in professional attendance.

In any consideration of precautions against malpractice claims the keeping of good medical case records must be emphasized. It is desirable that a physician ask himself, from time to time, what he would wish to have in the record in the case under treatment in the event that he should later be called on to justify his conduct of the case in court. "Ideal" records should be kept in every case: records that would be presentable when offered in court; records that clearly show what was done and when it was done; and records that indicate that nothing was neglected and that the care given fully met the standard demanded by the law. If a patient discontinues treatment before he should or fails to follow instructions the record should show that fact. A good method is to file a carbon copy of the letter sent to the patient advising him against the unwise course. Although there is a legal presumption that a letter that has been mailed has been received by the addressee, there is no presumption that a letter has been mailed. The record should also contain, of course,

the laboratory reports, consultants' reports and certain miscellaneous forms that are necessary or desirable in particular cases, such as consent for operation, consent for autopsy, copies of reports required by law and acknowledgment of hazards of particular procedures (shock therapy, fever therapy and x-ray therapy).

Consent for operation must always be obtained. Any adult in a clear state of mind may authorize operation on himself. Oral consent might be considered sufficient, but because of the difficulty in proving that it was given, the physician should invariably require a witnessed consent in writing. If the patient is a minor (that is, a person under the age of twenty-one) consent is generally obtained from parent or guardian. If the patient is mentally incompetent the consent of the one who stands in the position of guardian is required.

When an operation is made compulsory by law (such as vaccination, or sterilization under eugenic sterilization statutes), the law furnishes the consent.

If an operation is unlawful, consent to its performance does not absolve the surgeon from liability. For example, all state statutes define the crime of abortion. In many the provision is that any abortion except one necessary to preserve the life of the woman is a crime. In some, the wording is "necessary to save the life of the woman"; in 7 the statute reads "preserve her life or that of her child." In 6 states this additional clause is found, "or abortion advised by two physicians to be necessary for that purpose." Four other states make the same provision on the basis of one physician. Abortion laws are highly varied. At the extreme the statute of 1 state provides that any abortion is a crime.

A physician is well advised to be cautious and not to perform an abortion without first calling in a reputable consultant and obtaining a concurrence of medical opinion on the necessity. An excellent practice now common in major hospitals is that of requiring the approval of a special committee of the staff before therapeutic abortion can be carried out in the institution.

In an emergency that demands immediate action for the preservation of the life or health of a patient and in which it is not practicable to obtain his consent or the consent of anyone authorized to speak for him, it is the duty of the attending physician to perform without consent such operation as good surgical practice demands (48 C. J. 1131).

If sterility is likely to result from the operation contemplated explanation of that probability should be made, and a signed authorization should generally be obtained from both spouses. On the other hand there should be no promise or guarantee that the patient will be sterilized as the result of the procedure undertaken.

The individual physician must obtain consent to perform a post-mortem examination. This consent, too, should be in writing and sufficiently comprehensive to allow the removal of any tissue necessary in the examination. In several states it is criminally illegal for any person to perform an autopsy without having first obtained the written authorization of the coroner or other authorized public officer or of the person who has the right of disposition of the body.

If a physician attempts to justify his failure to continue in attendance on a patient under the claim either that the patient discharged him or that he withdrew from the case, the burden of proving the statement, so the courts have held, will be upon him. If he is discharged by a patient or withdraws from a case a physician should therefore invariably confirm the event in writing and file a carbon copy with the case record.

An examination of malpractice suits reveals the significant fact that these claims arise almost invariably out of the first course of treatment. In other words it is rare indeed for an old patient, unless the action is justified, to file a suit against his physician. It follows that the physician should be especially "malpractice conscious" in dealing with the new or casual patient.

Conclusion

The majority of malpractice actions can be avoided by scrupulous attention to the requirements of good medical practice. There will be few cases of injury resulting from the actions of misguided or malicious patients when practitioners understand fully how to protect themselves under the law. Prevention is the best defense against suits for malpractice.

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MEDICAL PROGRESS

GASTROSCOPY*

Contributions to the Diagnosis of Benign and Malignant Lesions of the Stomach

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BOSTON

GASTROSCOPY is a valuable procedure in differentiating benign from malignant lesions of the stomach but is nevertheless only an adjunct to detailed history taking and physical, laboratory and x-ray examinations. It can sometimes establish a diagnosis, particularly in the gastritides, when other diagnostic methods have failed. Much of the uncertainty and speculation concerning enlarged gastric rugae demonstrated by x-ray examination has been eliminated since its introduction; when a lesion can be seen at gastroscopy, a precise anatomic diagnosis can be made.

From October, 1950, to September, 1953, I performed gastroscopic examination in more than 300 patients, some more than once, in various hospitals of greater Boston. The use of a flexible operating gastroscope[1, 2] has also made it possible to scarify the gastric wall with a polyethylene tube and take multiple specimens for biopsy, as well as aspirate secretions, with minimum discomfort to the patient.

METHOD

Preparation of the Patient

If rapport has been established between doctor and patient, gastroscopy should not be a painful experience. As in other endoscopic procedures, it is essential that all attendants reassure the patient and emphasize the necessity of the procedure. Adequate preparation for a satisfactory examination of the average person is assured if the patient gets a good night's sleep, induced by a barbiturate if necessary, and receives Seconal Sodium and Demerol Hydrochloride one and a half hours before gastroscopy; to depress bronchial secretions, atropine is given half an hour before the procedure. No local anesthetic is used.

The patient is placed in the left lateral position with two or three flat pillows under his head. A head holder is not used. The flexible operating gastroscope is passed through the mouth and esophagus, and into the stomach.

Ten minutes is the average time that elapses before the patient becomes very restless. Scarification of the mucosa, aspiration of secretions and taking of specimens for biopsy so narrow the actual time available for intragastric observation that the prime study of the gastroscopist is necessarily focused on areas questioned by the radiologist. As in fluoroscopy, however, even a fleeting observation of a tonus change or a peristaltic antral cycle in an area under suspicion may be adequate for ruling out an infiltrating lesion. Inflation and deflation of the part of the stomach under question may also help, by determination of distensibility or pliability of the mucous membrane.

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THE GASTROSCOPIC PICTURE

Effect of Gastric Tonus

Gastroscopic observation of the presence or absence of tonus changes in the stomach can be of considerable help in distinguishing between benign and malignant ulceration of the stomach. Gastric tonus is here defined as a change in the smooth-muscle layers. The change in contour follows the variation in contraction and relaxation of the smooth-muscle layers of the gastric wall caused by peristaltic waves or segmental spasm.

As seen gastroscopically, peristaltic waves normally start at the incisura and are usually propelled to prepyloric closure in cycles of five to twenty seconds. Antral peristaltic activity, which is limited to the distal third of the stomach[3-6] (Fig. 1), is sometimes not seen in the normal stomach.

Segmental tonus changes are disorganized, nonrhythmic contractions and relaxations that occur at all levels of the stomach, in cycles averaging two to five minutes. Areas of segmental tonus changes or spasm are rare but when present may aid in ruling out an infiltrating lesion. Figures 2 to 7 demonstrate such changes in different parts of the stomach in the normal, ulcerated, gastritic, or postoperative subtotally resected stomach, and rigidity in the infiltrated or neoplastic stomach.

Gastric Mucosa and Secretions

The mucous membrane is everywhere smooth, pink, glistening and intact. Apparent changes in color intensity, instead of being true variations, may be due to a falling off in illumination or to a particular angle of observation. Toxic, thermal or psychic stimuli, among other factors, may affect the color. Variations in mucosal color are not easy to evaluate. Patients without organic disease have come to gastroscopy with evidence of psychic strain of various degrees, and yet examination of most of these patients has shown no mucosal hyperemia or edema. The gastroscopic picture is presumably not confused by psychogenic factors.

Mucosal secretory activity cannot be observed through the gastroscope, but the mucous lake is seen to increase during the examination. A clear, colorless mucus covers the mucosa everywhere, and patchy, opaque, white, tenacious fluid can be seen on crests of folds. Swallowed mucus is seen in strands, looking like saliva, with its foamy characteristic. The lake of mucus in the fundus may contain mixtures of these secretions, or it may be blood stained from hemorrhage or gastric biopsy.

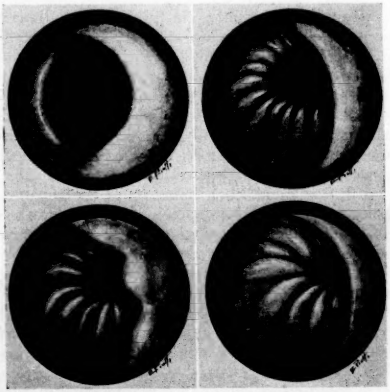

FIGURE 1. *Views of a Normal Antrum and Pylorus. Propulsive peristaltic waves start near the incisura and proceed in a pumplike action to the prepyloric or pyloric closure. Such smooth-muscle activity helps to rule out an infiltrating lesion in a spastic or irregular antrum observed at x-ray examination. The pylorus appears as a distinct muscular sphincter in the left upper view.*

Mucosal Pattern

During the contracted state of the stomach, numerous rugae appear, for the most part in a longitudinal direction, and most noticeably toward the pyloric end of the organ and along the greater curvature. These folds are entirely obliterated when the organ becomes distended.

Antrum and Pylorus

The antrum is the only part of the stomach that gastroscopically exhibits rhythmic motility. It may be necessary to observe the antrum for several minutes before a wave is seen to begin. Peristalsis starts as a shallow wave at approximately the angulus and rolls symmetrically toward the pylorus, becoming a strong contraction ring and then relaxing in the prepyloric area, where the pylorus may be seen. During the course of a peristaltic wave, the lesser curvature of the antrum can be visualized except for a small area distal to the angulus.

Cole[7-9] has studied peristaltic waves in the human stomach by means of serial x-ray photographs. He describes the peristaltic movement as a band of constriction that becomes strong in the region of the incisura angularis and ends 1 or 2 cm. above the beginning of the pyloric canal. The gastric wave travels more rapidly over the greater curvature than over the shorter distance of the lesser curvature, and the constriction on the lesser curvature on reaching the incisura angularis "marks time" whereas that on the greater curvature continues on through the antrum.

Cole compares these rhythmical alterations in the shape of the stomach to the cardiac cycle. The period from the moment a particular shape appears until the moment that the form reappears constitutes a complete cycle of gastric movements. Gastric systole is that phase marked by deep indentations made by the constricting rings and a reduction in gastric capacity. Gastric diastole is the period during which the contractions show less tendency to deform the gastric outline. The average time for the complete cycle is twenty seconds.

In the normal stomach or in one without an infiltrating lesion that penetrates the muscular layers antral peristalsis and areas of segmental tonus changes may be stimulated by air that is introduced and then released, as well as by the taking of a biopsy specimen with forceps through the gastroscope (Fig. 2).

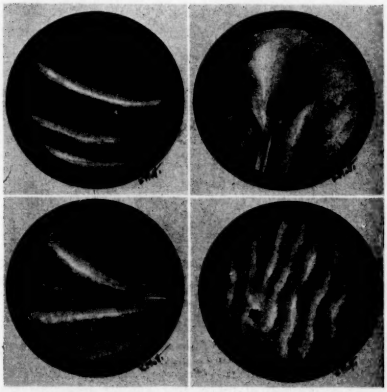

FIGURE 2. *Views of a Normal Middle Portion of the Stomach Proximal to the Incisura, Where Three Normal Folds Are Observed. After biopsy, under direct vision, the same area exhibits nine smaller folds. This effect may be the result of a stimulus to the muscularis mucosae.*

Angulus, or Incisura Angularis

The angulus divides the body, or pars media, of the stomach from the antrum, and is an anatomic feature that should be identified at each examina-

tion. This landmark can be seen from all parts of the stomach except when the objective of the instrument is in the fundus or distal to the incisura. It appears as a large, semilunar fold arising on the anterior wall, projecting into the lumen of the distal third of the stomach, crossing the lesser curvature and descending on the posterior wall (Fig. 1).

Pars Media

The body of the stomach extends from the fundus to the incisura angularis on the lesser curvature. It is a narrow, tubelike structure when empty and is capable of great distention. The lesser curvature and anterior wall of the body are usually flattened, but rarely two or three shallow folds, easily effaceable by inflation, run parallel to the lesser curvature. Aschoff's magenstrasse does not exist gastroscopically. The posterior wall exhibits numerous folds that can easily be distended with air.

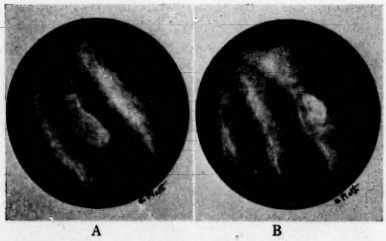

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FIGURE 3. *Benign Ulcer on the Posterior Wall in the Middle Portion of the Stomach with the Patient in the Left Lateral* (A) *and Right Lateral* (B) *Positions.*

The position of the gastroscope remains unchanged. The ulcer crater appears to have changed in size, shape and position with respect to the mucosal folds. This change indicates a smooth-muscle alteration of the segmental type in the middle part of the stomach, where no propulsive waves are generally visible.

A standard anatomy textbook[10] states:

> . . . Along the lesser curvature are three or four long, narrow, very constant ridges, which pass without a break from the oesophageal orifice towards the pyloric part of the stomach. . . . They are parallel to one another, and are apparently never obliterated. Between them are deep furrows, which form channels leading from the oesophageal orifice to the pyloric portion. At the junction of the body and pyloric portions, at the level of the sulcus intermedius, is often a transverse fold of mucosa which is of some size, termed the plica pre-pylorica.

Reference is then made to a photograph of the stomach after death. The stomach removed postmortem or surgically has apparently been fixed in a state of contraction. Gastroscopic observation of the intact normal stomach in a living human being shows none of the landmarks described. No permanent folds, deep furrows or ridges in the uninfiltrated stomach have been observed by the gastroscopist.

The same anatomy textbook states: "When the stomach is empty, all three outer coats, which are extensile, contract and the mucous coat is thrown into numerous folds or rugae which project into the interior." This would make the mucous membrane a passive coat dependent on contraction and relaxation of the three outer coats of the stomach. It has been shown, however, that the muscularis mucosae affects the pattern of mucosal relief quite independently of the main muscular coat.[11, 12] The formation of high and close folds of the antral mucosa may occur more easily with a simultaneous contraction of the main muscular coat, but the degree of contraction of this coat does not produce a corresponding pattern of mucosal relief. Any stage of contraction of the muscular coat can be associated with a variation in mucosal pattern, from a smooth, flat surface to a complicated pattern of folds. This is a characteristic manifestation of the muscularis mucosae.[12]

A diffuse constriction of a part of the antrum or antral narrowing may be seen by the radiologist, but under conditions of gastroscopy it relaxes and thus permits a view of the antrum and peristaltic waves contracting and relaxing in the region of the pylorus.

The inability to visualize more than a few antral craters constitutes an important gastroscopic deficiency.[13] And since the biopsy instrument has not usually been successful in reaching questionable areas of the antrum, particularly areas of submucosal infiltration, identification of the antrum and its tonus changes becomes extremely important. If antral pliability, distensibility, peristalsis and pyloric closure can be visualized unseen ulcers are benign as a rule.

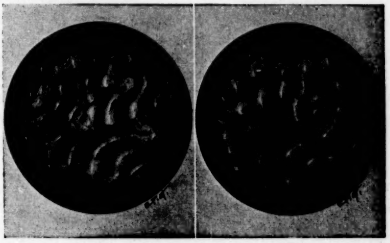

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FIGURE 4. *Posterior Wall in a Patient with Chronic Hypertrophic Gastritis, Showing Thickened, Tortuous Folds* (A), *Fusiform and Tightly Packed, Which Are Easily Distensible with Air, and a Slow Segmental Tonus Change in the Form of a Shallow, Pseudopouch Effect* (B).

Cardia

As the gastroscope is withdrawn, a prominent mucosal shelf that divides the esophagus from the stomach is seen. The sharp transition of large red-

dish-orange folds of the fundus and cardia to the gray, flat mucosa of the esophagus is clearly defined.[14] The fundus is the dome-shaped portion of the stomach lying above the cardiac orifice. Inflation in this part has the least distending effect and remains so, even though the antrum and middle portion are fully distended. During the examination the fundus is the most dependent part, in which all secretion accumulates and forms the lake of mucus.

Gastric Ulcer

Ulceration of several different types occurs in the stomach. Repair of ulceration may take place in the stomach as readily as elsewhere in the body, but excessive motility and hydrochloric acid and pepsin in its secretion may retard healing, prevent repair and cause enlargement of the original lesion.[15]

A hemorrhagic erosion is an ulceration that follows a miliary hemorrhage and is usually associated with multiple similar lesions most frequently seen in the fundus and limited to the mucosa. Such erosions can heal rapidly within a few days, and yet actively bleeding multiple erosions may cause massive gastrointestinal hemorrhage. They are not demonstrable by x-ray examination and may be associated with any of the gastritides, chronic ulcer or carcinoma.

Acute ulcerations are found in all parts of the stomach but most often in the fundus, on the posterior wall, and in the prepyloric region. They are superficial but extend deeper than erosions. Their edges are sharply margined, and the adjoining tissue shows a discrete area of hyperemia. An ulcer of this type may heal within a week, leaving no scar. Free hydrochloric acid may be absent.

The chronic ulcer may be round or oval. It is most commonly located on the posterior wall between the fundus and pylorus near the lesser curvature. Its edges are slightly indurated and sharply defined. The base of the ulcer is usually clean, and the sides slope toward the deepest point. Gastroscopic inflation can spread out the crater and adjacent folds and permit visualization of early nodularity, stiffness or peripheral infiltration (Fig. 3).

The motility features described and illustrated above are of considerable help. An ulcer crater may be observed obliquely when adjacent tissues contract. The extent of distensibility and pliability of the involved area will help to determine if the lesion is benign.

Gastritis

Gastritis is the most common disease of the stomach according to gastroscopic reports from all over the world. It is defined as an inflammation of the stomach.[2]

Acute Gastritis

The acute form of gastritis may be caused by drugs, ingestion of large amounts of alcohol (rarely), local and systemic infections, oral intake of corrosive substances and hematogenous effects of toxic substances. The mucosa presents a generalized hyperemia, edema, sometimes erosions, petechiae and hemorrhage. There is no purulent exudate.[14]

Acute and chronic gastritis may both be present in the same stomach and associated with gastric or duodenal ulcer and benign or malignant lesions of the stomach.

Chronic Gastritis

According to Schindler's[16] statistics on gastroscopically observed gastric disease in the United States and Germany, the chronic form has an incidence of approximately 45 per cent, which parallels my findings.

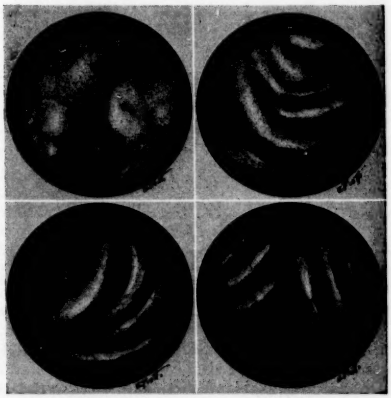
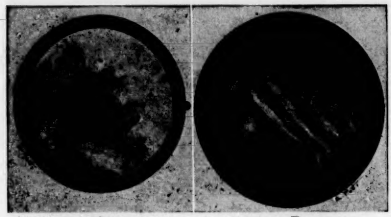


Figure 5. *Views of a Subtotally Resected Stomach after Operation. The upper left view shows a patulous gastrojejunal stoma, looking from the stomach into normal jejunal folds. The upper right exhibits, just below the stoma, a series of concentric folds, which when moderately inflated with air show pseudopouch effects of slow smooth-muscle changes. These changes help to rule out an infiltrating lesion in the residual stomach.*

The etiology of chronic gastritis is unknown.

Chronic superficial gastritis. The patient describes a vague epigastric pain, rarely ulcerlike and more frequently not relieved by food. Usually of only a few months' duration, the complaint is sometimes present for many years. An indefinite feeling of pressure after a meal is often associated with nausea, severe weakness and, sometimes, vomiting. Epigastric pain or pressure may cause restlessness at night. The patient feels better fasting or taking only sips of water on bed rest for a day or two. Aluminum hydroxide has also been used and affords considerable relief. The patient does not give the impression of being seriously ill. On abdominal palpation epigastric and periumbilical tenderness may be the only finding.

X-ray examination usually reveals a normal upper gastrointestinal tract, with no signs of superficial gastritis. The clinical diagnosis can be made only by gastroscopic examination, the characteristic findings being simply a purulent exudate and patchy hyperemia. The areas of redness, which may be seen in any part of the stomach, are not circumscribed but, rather, fade out gradually at the borders.[14] The characteristic purulent exudate is thin, gray and opaque, covering smooth surfaces and collecting between rugal folds. Erosions and free bleeding may be present to the point of massive hemorrhage. Although the mucosa bleeds easily,



A B

FIGURE 6. *Polypoid Adenocarcinoma, Showing the Immobile Polypoid Projections Into the Midgastric Lumen* (A) *and a Nonpliable, Gray Mucous Membrane* (B) *on the Posterior Wall Proximal to* A.

the taking of a specimen for biopsy has never produced hemorrhage.

On bed rest, a bland diet, and occasional fast periods, most of these patients get well, and the mucosa returns to a normal appearance, recurrence being rare. Schindler[17] reports that chronic atrophic gastritis develops in approximately 20 per cent of such cases.

Chronic atrophic gastritis. Chronic atrophic gastritis, which occurs in young adults and middle-aged people, is usually of many years' duration. Epigastric pressure directly after meals, belching and the ability to take only small meals are the gastric complaints. Extreme nervousness and exhaustion are common symptoms. Many of these patients live to advanced years with this disease. Some have had cholecystectomy, the gall bladder sometimes grossly diseased, with no postoperative improvement in their distress.

These patients give no evidence of combined-system disease. X-ray examination is usually negative. The bone marrow is normal, as is the hematologic picture. Even in the absence of pernicious anemia the tongue may be smooth. Free hydrochloric acid is found in those exhibiting superficial and atrophic gastritis, but in most cases of atrophic gastritis, histamine achlorhydria is the rule.

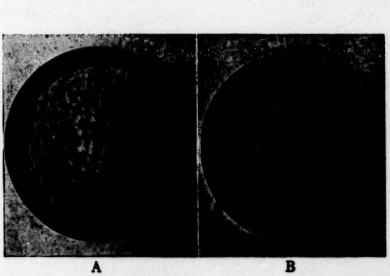
The gastroscopic picture is that of a thin, pale-gray, smooth mucosa in which a fine blood-vessel pattern is easily seen. Atrophic areas may be patchy or diffuse. Small superficial hemorrhagic erosions occur, but less often than in other forms of chronic gastritis. The early detection of polyps and pseudopolyps to prevent tumor formation in these patients is the responsibility of the gastroscopist.

The course of the disease is usually that of an irreparable end stage of gastritis. Protracted therapy with parenteral injections of liver or vitamin B_{12} has made no change or improvement in the mucosa, nor does free hydrochloric acid return.

Some of these depressed, exhausted patients somehow become accustomed to their indigestion.

Chronic hypertrophic gastritis. This disease is found at any age but most often in elderly patients. The duration is usually many years, sometimes ten or even twenty. Milk, food or antacids afford little or no relief from the severe epigastric pain, and episodes of night pain are frequent.

Physical examination is frequently nonrevealing. Some radiologists, on the basis of thick mucosal folds and increased secretion, make a diagnosis of hypertrophic gastritis. Because the thickness of the folds depends on the tonus of the muscularis mucosae, the thickness of submucosa and the tonicity of the muscularis propria, many radiologists believe



A B

FIGURE 7. *Diffuse Gastric Carcinoma, with Pathologic Ulcer, Showing a Rigid, Cobblestonelike Mucous Membrane* (A) *of the Anterior Wall and the Irregular Necrotic Margin and Base of a Carcinomatous Ulcer* (B) *in the Cardiac Portion.*

that more valuable information can be obtained from gastroscopic than from radiologic examination; it is undeniable that these are complementary aids in the study of diseases of the stomach.[18]

In hypertrophic gastritis the gastroscopist sees a dull, velvety, verrucous mucosa, which may be patchy or diffuse. The folds may become segmented and then nodular. In the late stages, the short, stiff, verrucous elevations become so rigid as to make differentiation from a malignant lesion impossible. Even if the biopsy or aspirate is negative, or only gastritis is indicated, surgery is advised. Sometimes, however, even hypertrophic

gastritis of such severity may yield segmental tonus changes (Fig. 4) and thereby help to rule out malignant infiltration.

Hemorrhagic erosions and superficial acute ulceration are frequently seen during acute painful episodes in chronic hypertrophic gastritis. Sometimes they heal within a few days on conservative management, but the course is ordinarily much more protracted than that of chronic superficial gastritis. The patient does not, however, exhibit the features of depression that are characteristic of chronic atrophic gastritis.[17]

The "Postoperative Stomach"

In the past quarter-century the "postoperative stomach" has been an increasing occurrence. The gastroenterologist rarely sees the many patients who are completely free of distress and pain after operation; he does see those who are not cured, and he may easily get a false impression of the incidence of postsurgical complications.

The patient with a gastroenterostomy shows all the features of the intact stomach as well as the stoma leading to the closely packed, brown, circular folds of the adjacent jejunum. In the subtotally resected stomach propulsive peristaltic waves are never seen. Tonus changes sometimes appear as an outpouching of various shapes (Fig. 5); depending on the suture line, the border of the stoma may present many shapes. Rarely smooth, it most commonly has a polypoid appearance through which the brown, circular folds of the jejunum are unmistakable. The stoma appears patulous and noncontractile in most of the examinations.

Gastrojejunal ulceration may be single or multiple, occurring on the gastric or on the jejunal side of the stoma. The anastomotic ulcer, when visible, may be superficial or deep.

Gastritis of all types may occur. During the first month after operation the mucosa shows considerable edema and red folds frequently bathed in purulent exudate.[14] After this period, most stomachs show only the effects of surgery. Gastritis present before operation may persist and become intensified gastroscopically even though the patient is asymptomatic from time to time. Combinations of superficial, atrophic and hypertrophic gastritis are much more frequent than ulcer after operation. Gastric aspiration usually affords some relief. Hemorrhagic mucosal erosions or acute superficial ulceration in various states of healing is most common in unexplained massive gastrointestinal bleeding.

Carcinoma frequently recurs after resection. The characteristic rigid wall and nonpliable gray mucosa may or may not yield a positive specimen at biopsy or on exfoliative cytology.

Rigid Lesions of the Stomach

Differential Diagnosis of Severe Gastritis and Carcinomatous Infiltration

Occasionally, tonus changes are lacking in the normal stomach. In the normal stomach without tonus changes, however, there is effacement of the mucosal folds or distensibility of the gastric wall with air inflation.

Infiltrating lesions may begin in the margin of an ulcer or extend from the mucous membrane to a localized and small portion of the muscular coat; such lesions are rare and do not disturb any of the motility features. In the gastric wall a rigid lesion will prevent tonus changes of the propulsive or segmental types, interfere with distensibility of the gastric wall and degrade the pliability of the mucosal folds. More commonly, infiltration involves the entire muscular coat and muscularis mucosae beneath an intact mucosa. This process is not static or circumscribed. It may involve the antrum, pars media, cardia or fundus, alone or together, and may even extend into the lower end of the esophagus. If only the antrum appears rigid, all the motility features may be present in the mid-stomach whose muscular coat is only partially infiltrated.

An infiltrating lesion sometimes inverts the proximal portion of the antrum, hiding the lesion, the incisura angularis and the antrum itself. A satisfactory view of the distal part of the antrum, identification of the angulus and visualization of active antral peristalsis are therefore of critical importance. Multiple polypoid or ulcerative lesions associated with rigidity in the antrum or angulus should be regarded as an infiltrating lesion and surgery advised even though biopsies and aspirate reveal gastritis or normal tissue.

Differential Diagnosis of Benign and Malignant Ulceration

Approximately 10 per cent of gastric ulcers under observation are carcinomatous. The alert diagnostician will ensure early detection and prompt treatment by using all clinical means at his disposal for precise diagnosis. He will not omit gastroscopic examination, gastric biopsy and study of the exfoliative cytology of freshly aspirated gastric juice.

The benign ulcer is a sharply margined crater with a clean, white base, without evidence of rigidity, nodularity or irregularity. An associated gastritis may limit tonus changes and distensibility slightly, but even a severe gastritis will not produce the induration that is characteristic of a rigid pathologic ulcer. The effaceability of gastric rugae with inflation is characteristic, and helps to differentiate the benign lesion from the immobile carcinomatous lesion.[14]

A carcinomatous ulcer usually exhibits a necrotic base of many colors, sometimes bleeds eccentrically and has overhanging margins that are frequently

steep, nodular, irregular and rigid. The adjacent mucosa is frequently rigid and nonresponsive to air inflation, and the gastric wall is distorted. Schindler[19] considers deep mucosal hemorrhages to be indicative of the benign nature of a gastric ulcer even if the ulcer is not visible; contrariwise, multiple deep mucosal erosions were easily seen all over the midstomach and cardia in several cases of malignant gastric ulcer. On the basis of such conflicting experiences the presence of mucosal erosions is of no help, even indirectly, in diagnosis. It is most important to see the lesion.

The most common tumor of the stomach is the carcinoma, which may grow rapidly and project in papillary or cauliflower-like masses into the lumen of the organ or may undergo more or less extensive ulceration. Frequently, it is the scirrhous type, which grows slowly and forms a local induration or spreads out gradually until the entire wall of the stomach is contracted into a small part of its normal area (Fig. 6 and 7).

Technics

Gastric-Aspiration Procedure

One can safely scarify the mucosa under direct vision by scraping the gastric wall with a polyethylene tube through the operating gastroscope; during this procedure, desquamated and denuded

Figure 8. *Gastric Aspirate, Obtained without Trauma, Stained by Papanicolaou Technic.*
Nuclear enlargement, diminished cytoplasm and variation in nuclear shape are characteristics of tumor cells.

mucosa and muscularis mucosae are aspirated and immediately fixed for cell block (Fig. 8). A suction apparatus is attached to the polyethylene tube, and between them a stoppered specimen tube with inlet and outlet arms containing a fixing solution is arranged so that the exfoliative gastric contents are immediately fixed — formalin (in 10 per cent solution) yields satisfactory results. In over 300 cases observed, there has not been a single case of perforation or excessive bleeding.

Gastric Biopsy

Up to the present histologic examination of the stomach has been based on specimens taken at operation and at autopsy. The very source of the material introduces variables that affect the accuracy of the study since the cause of death and postmortem changes may contribute to the histologic picture. Also, serial observations are obviously impossible because of the nature of the material.[20-23]

The channel in the flexible operating gastroscope makes it possible to take multiple specimens for gastric biopsy,[1] but the antrum and fundus of the

Figure 9. *Gastric Scrapings, Showing Pavementlike Arrangement of Tumor Cells in Sheets.*
There is a disproportion of nuclear cytoplasm, with nuclear enlargement and variation in shape, as well as prominent nucleoli.

stomach appear at present to be beyond the reach of the biopsy forceps.[24, 25] A diagnosis of a submucosal or intramural lesion is based on its gastroscopic appearance (Fig. 9).

It has been my experience over the past three years that tissue suitable for histologic diagnosis is easily obtainable when the lesion is diffuse or located in the body of the stomach. If the pathologist reports that the biopsy shows a carcinoma, the diagnosis is clear. If the biopsy is negative for cancer but the x-ray films disclose a questionable defect, cancer should not be considered ruled out. As corroborated by the pathologist's report on surgically removed specimens, a correct diagnosis has been made at gastroscopy in most cases in which biopsy has failed. Biopsy diagnosis in this series of gastric carcinoma has been 39 per cent positive. Because of technical difficulties, however, the method lacks accurate "siting." Its role at present is therefore limited in the differential diagnosis of localized lesions such as ulcer and carcinoma.

The differential diagnosis of diffuse gastric carcinoma, giant hypertrophic gastritis and lymphosarcoma is difficult. No diagnostic, clinical or laboratory data (including gastroscopic findings) are available to distinguish chronic hypertrophic gastritis from carcinoma. If biopsy is positive, however, the diagnosis is clear.

FIGURE 10. *Interstitial Infiltration by Lymphocytes and Monocytes, with a "Skip Area" on the Right with no Interstitial Infiltrate — Only Stroma and Capillaries.*

Normal mucus-producing epithelial cells are present at the surface. This histologic picture is characteristic of chronic superficial gastritis.

Chronic gastritis is characterized by a diffuse interstitial infiltration by chronic inflammatory cells.

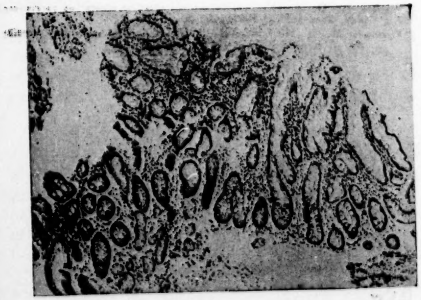


FIGURE 11. *Diffuse Interstitial Infiltrate of Chronic Inflammatory Cells.*

Mucus-producing glands are present throughout the entire thickness of the mucosa (intestinalization of the gastric mucosa). This picture is seen fairly frequently in chronic atrophic gastritis.

The stroma between the surface epithelium and glandular elements is infiltrated by lymphocytes, monocytes and plasma cells. In chronic superficial gastritis only the stroma near the surface epithelium shows an interstitial inflammatory infiltrate (Fig. 10). The lower half of the gastric tubules remains normal. The parietal and chief cells stain well. Rupture of a capillary plexus just beneath the surface epithelium may occur, with hematemesis and extravasation of blood into the stroma.

The biopsy in chronic atrophic gastritis is characterized by a variation in the stromal infiltrate. The full length of the tubule may become lined by mucus-secreting cells. The base may still show a few chief and parietal cells. Active proliferation of the foveolar cells produces tortuosity in the pits. This metaplasia is patchy, and abrupt changes from the gastric to the intestinal type can be seen in a single microscopical field (Fig. 11).

Biopsy specimens are not large enough to demonstrate hyperplasia of the folds characteristic of chronic hypertrophic gastritis, but the interstitial infiltration in this lesion extends down to the lower levels of the mucosa and even involves the adjacent muscularis mucosae (Fig 12). The biopsy is also an aid to clinical and pathological study in many diseases in which the gastric lesion is not the main feature. This is exemplified in cases of pernicious anemia and hemochromatosis.[21-23]

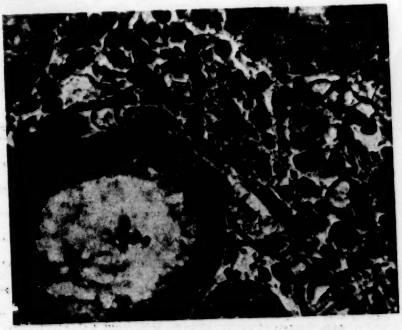


FIGURE 12. *Marked Interstitial Infiltration by Lymphocytes, Plasma Cells and Monocytes.*

Metaplasia of the glandular epithelium is seen. Note the congestion of a capillary bed. This is the classic picture of chronic hypertrophic gastritis.

SUMMARY AND CONCLUSIONS

Gastroscopic observation of the presence or absence of changes in the smooth-muscle layers of the stomach can help to differentiate benign from malignant ulceration of this organ.

Recurrent epigastric or periumbilical pain, usually aggravated by food, and a nonrevealing upper gastrointestinal series of x-ray films indicate the need for gastroscopic examination and gastric biopsy.

Detailed microscopical study of gastric biopsies and aspirate should be correlated with the gastro-

scopic picture in the final diagnosis of chronic gastritis.

A positive gastric biopsy or aspirate points to a definite diagnosis.

Negative tissue or a specimen indicating gastritis does not rule out carcinoma.

The patient with a gastric lesion can be observed more adequately by means of the gastroscope so far as diagnosis, therapy, prognosis and course of the disease are concerned.

The various gastroscopic fields reproduced in this paper were drawn by Miss Etta Piotti from preliminary sketches made during actual gastroscopic procedures.

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MEDICAL INTELLIGENCE

RESERPINE IN THE TREATMENT OF HYPERTENSION*

A Note on the Relative Dosage and Effects

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RECENTLY, *Rauwolfia serpentina* was introduced into this country for the treatment of hypertension.[1-3] This stimulated renewed chemical and pharmacologic studies on the drug, which had been known and used in India for many years. Reserpine, a pure alkaloid, was isolated and shown to have in animals the sedative and hypotensive effects characteristic of the crude drug.[4] This alkaloid was then tried in hypertensive patients and found to have actions that were clinically similar to those of the crude drug.[5, 6]

The purpose of the present paper is to report further observations on Reserpine,** especially of its dosage and clinical effects in comparison with those of *Rauwolfia* either as the crude drug†† or as an extract.‡‡

PROCEDURE

The patients either had been attending the Hypertension Clinic or had been followed in the private practice of one of us. They were well known, had been studied by the generally accepted methods of evaluating renal, cardiac and cerebrovascular hypertensive disease,[3] and were followed regularly at intervals of one to four weeks. In most of the 58 cases given Reserpine alone, control observations extended over several weeks or months and included at least one period of treatment with a placebo. Daily oral dosage of Reserpine varied from 0.1 to 8.0 mg., although the larger doses (above 1 mg.) were usually tried only for short periods. In many cases treatment with Reserpine was alternated with treatment with *Rauwolfia*, with a placebo or with no medication. In an additional group of 35 similar patients already being maintained on *Rauwolfia* with or without other hypotensive medication, Reserpine was substituted for the *Rauwolfia*. Finally a few patients were started immediately on Reserpine in combination with some other hypotensive therapy. In all, over 100 patients received the drug for periods of four to fifty-two weeks.

RESULTS

In 58 patients given Reserpine alone, the average of all the control blood-pressure measurements recorded during no (or placebo) treatment was 191 systolic, 109 diastolic, and the average pulse rate was 85. During treatment with Reserpine the averages were 167 systolic, 94 diastolic, and 75 respectively. Thus, it appears that Reserpine is an agent with modest hypotensive and bradycrotic actions. Its effects were about the same as those of *Rauwolfia*, which given alone in 39 patients caused changes in average blood pressure and pulse rate from 192 systolic, 112 diastolic, to 165 systolic, 95 diastolic, and 82 to 70 respectively.[3]

Reserpine also had side effects like those of *Rauwolfia*. In order of frequency these were sedation, nasal congestion, weight gain, diarrhea, nightmares and depression. None were regarded as serious or toxic. As after the crude drug, these symptoms could always be lessened or eliminated by reduction or interruption of the medication. These actions, also like those of *Rauwolfia*, appeared within one to three weeks, persisted throughout treatment (up to fifty-two weeks) and disappeared one to three weeks after the end of treatment.

The total daily dosage of Reserpine tolerated by different patients over a period of weeks varied between 0.1 and 1.0 mg. This compared with total daily dosages of the crude drug (or its equivalent in the form of an extract) of 100 to 1000 mg., as previously observed.[3, 6] This 1:1000 proportion was further borne out in the patients maintained on *Rauwolfia* by the substitution of 1 microgm. of Reserpine for each milligram of *Rauwolfia* previously given. In 35 patients the substitution was tolerated at or near this proportionate dosage. It also appeared that in these patients 0.1 mg. of Reserpine was not less active in any respect than 100 mg. of the crude roots available to us. Thus, patients in whom the dosage of *Rauwolfia* had been already raised to the maximum that they could tolerate

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**Kindly supplied as "Serpasil" by Ciba Pharmaceutical Products, Summit, New Jersey.

††Raudixin, available from E. R. Squibb and Sons, New York City.

‡‡Rauwiloid, available from Riker Laboratories, Incorporated, Los Angeles.

could tolerate little more than one thousandth of this dose (by weight) of Reserpine given in substitution for the *Rauwolfia*. In all but 1 of the 35 patients in whom it was so substituted for *Rauwolfia*, Reserpine was at least as hypotensive and bradycrotic as the *Rauwolfia* had been.[6] (In this case the crude drug has been reinstituted, and the substitution will be tried again, since it was not conclusive that the rise of blood pressure after substituting Reserpine was due to the change in medication.) The side effects of Reserpine such as sedation, nasal congestion, weight gain and diarrhea not only were identical with those of *Rauwolfia* but also occurred in relatively small dosages in the same few patients who had had these effects on relatively small dosages of *Rauwolfia*.

In hypertensive patients Reserpine, like *Rauwolfia*, had clinically desirable effects in addition to hypotension and bradycardia. It relieved headache, dizziness and fullness in the head, decreased palpitation, and lessened nervousness, irritability and anxiety. Like *Rauwolfia* it also appeared to moderate some of the undesirable effects, particularly the tachycardia, of hydralazine as well as some of the unpleasant effects of other hypotensive agents. This made it of value in combination drug treatment.[5-7]

For these reasons the pure alkaloid, Reserpine, is considered the chief active principle of crude *Rauwolfia*, at least when given in oral dosages that can be tolerated by hypertensive patients for prolonged periods. Therefore, we are now substituting Reserpine for crude *Rauwolfia* in all patients on drug treatment for hypertension to provide greater experience with its long-term effects.

Summary

Reserpine, a pure alkaloid of *Rauwolfia serpentina*, when given in a daily oral dosage of 0.1 to 1.0 mg. to over 100 hypertensive patients for four to fifty-two weeks, appeared to have all the actions of the crude drug as used clinically. It is therefore regarded as the chief active principle of *Rauwolfia*.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40111

PRESENTATION OF CASE

First admission. A seventy-one-year-old gardener was admitted to the hospital because of pain in the right eye.

The patient was apparently well without complaints until four or five months before admission, when irritation of both eyes was noticed. Two weeks before entry the right eye became painful. At about the same time that he noted the eye difficulties, he had skin eruptions over the head and face that gradually became generalized.

Physical examination revealed a thin, underdeveloped white man with circumscribed erythematous, slightly raised, occasionally crusted single or multiple confluent lesions on the scalp, face, back, chest, axillas, umbilicus and parts of the arm. There was light perception only in the right eye and 4/300 vision in the left. There was blepharospasm and edema of the lids, with some narrowing of the palpebral fissure; the conjunctiva was bound down bilaterally with adhesions of the canthi and fornices (Fig. 1). The chest was clear to percussion and auscultation; the heart was normal.

The temperature, pulse and respirations were normal. The blood pressure was 150 systolic, 80 diastolic.

Urinalysis was normal except for the sediment, which was loaded with white cells. Examination of the blood showed a hemoglobin of 11.8 gm. per 100 cc., and a white-cell count of 4700, with 72 per cent neutrophils, 19 per cent lymphocytes, 6 per cent monocytes and 3 per cent eosinophils. Culture of the conjunctiva demonstrated a heavy growth of diphtheroids.

Heparin drops were tried in the eye to no avail. The right eye seemed worse, whereas the left remained about the same. A plastic operation on the right eyelid was performed to do away with trichia-

sis. The patient was subsequently discharged home to be followed in the clinic.

Second admission (six months later). After a course of chlortetracycline therapy with apparent

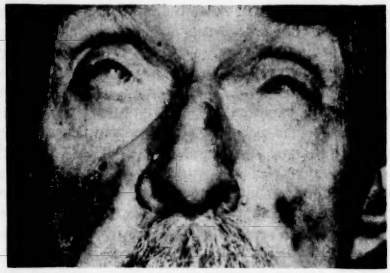

FIGURE 1.

subjective improvement he was readmitted to the hospital because of increasing impairment of vision

FIGURE 2. *Roentgenogram of the Upper Esophagus after a Barium Swallow.*

The esophagus is filled with barium and shows an anterior web at the level of the cricopharyngeus (upper arrow) and an area of stricture of the esophagus distally (lower arrows).

in the left eye. At this time the findings were as before except that the conjunctival changes were much more advanced.

After application of boric acid compresses the activity in the left eye diminished. The patient was then discharged without further treatment.

Third admission (three years and six months later). From the time of discharge, his sight progressively decreased until seven months after discharge, when he became totally blind. The scalp lesions apparently improved under boric acid shampoo although skin lesions on the face were still active. A year after discharge he complained of difficulty in swallowing, and examination revealed scars and crusts in the throat and tonsillar fauces. Biopsy of the soft palate was reported by the pathologist as showing "subepidermal bullae." A barium-swallow examination disclosed two constricted areas in

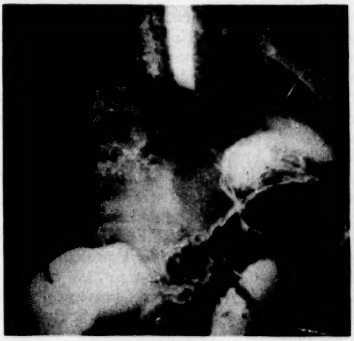

FIGURE 3. *Left Posterior Oblique Film of the Distal Esophagus and Stomach, Showing Conical Narrowing of the Distal Esophagus from Stricture (Arrows).*

Note also the presence of barium in the right lower lobe owing to aspiration at the time of the gastrointestinal study.

the upper cervical esophagus just below the hypopharynx (Fig. 2). There was also moderate conical narrowing of the distal esophagus. The patient aspirated some of the barium into the right bronchial tree (Fig. 3). On esophagoscopy a membranous web was seen stretching across the lumen of the esophagus, the lumen measuring only 2 or 3 mm. in diameter. Beyond this area the esophagus was apparently normal. Divulsion of the esophagus was performed, after which the patient was able to eat more easily. A second barium-swallow examination done a month later failed to demonstrate the constrictions previously described. Ten months later esophagoscopy and divulsion were again performed for recurrence of difficulty in swallowing. At this time the narrowed area had a lumen 3 mm. in diameter and exhibited considerable reddening and some edema. He was able to swallow fairly well for the next fifteen months, after which he required

further esophagoscopy and bouginage. Findings in the esophagus were as before. The skin lesions during this time had fluctuated in activity.

Physical findings were unchanged; the skin lesions were confined mainly to the face. The patient was started on 20 mg. of ACTH intravenously for thirteen days and 30 mg. for fourteen days, followed by considerable change in the skin lesions and less difficulty in swallowing. A biopsy of a skin lesion during this admission was reported as showing subepidermal bullae with no acantholysis and with numerous eosinophils in the vesicle and corium.

Final admission (three months later). In the interval, he seemed to be doing fairly well until a month after discharge, when he again noted soreness in the mouth, increasing difficulty in swallowing and loss of weight. These symptoms apparently became gradually worse, and three days before entry cough, chest pain and shaking chill, followed a day later by fever, developed. On the day of admission he was unable to swallow anything.

Physical examination showed bullous lesions in the mouth and pharynx. The chest was emphysematous, and expansion poor. There were dullness and bronchial breath sounds in the right base and crackling rales in the left. The heart was normal. There were several areas of scarring and erosion over the face.

The temperature was 102°F., the pulse 100, and the respirations 25. The blood pressure was 100 systolic, 50 diastolic.

Urinalysis disclosed a specific gravity of 1.021, a ++ test for albumin and a + test for sugar, with 5 white cells and hyaline casts per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 12.5 gm. per 100 cc. and a white-cell count of 7700. The sodium was 131 milliequiv., the potassium 3.0 milliequiv., the chloride 98 milliequiv., and the carbon dioxide 24 milliequiv. per liter. The nonprotein nitrogen was 29 mg. per 100 cc. Throat culture grew out abundant *Staphylococcus aureus* and rare pneumococci.

Intravenous infusion of 5 per cent dextrose in water was begun, and penicillin and streptomycin administered. On the second hospital day, the temperature dropped to 99°F. An ear, nose and throat consultant found multiple bullous lesions in the mucous membrane of the oral cavity and pharynx but no obstruction of the nasal passages. On the third hospital day, the patient suddenly died.

Differential Diagnosis

Dr. Herbert Mescon*: In summary this seventy-one-year-old man had bullous lesions of the mucous membranes of the esophagus, the oral cavity, the conjunctiva and the skin, in addition to esophageal narrowing, and died with findings suggestive of pneumonitis. The bullous diseases that I must consider in the differential diagnosis of this case fall into the following categories: dermatitis herpetiformis; epidermolysis bullosa; pemphigus; pemphigoid (chronic benign pemphigus); erythema multiforme, which includes the syndromes of Behçet, Stevens–Johnson and Reiter and ectodermosis erosiva pleuriorificialis; and bullous lupus erythematosus. The clinical classification of these disorders and their differentiation from each other is extremely difficult. Many of them do not have distinct histologic features, and the etiology of most is unknown. The same bullous condition may be put into one category in one city and into another category in another city. In the past the so-called "splitter" tended to give each new variation of the bullous diseases a different man's name or a different disease name. Lately the so-called "lumpers," in the belief that there is no proof that the disorders observed are not merely variations of the same disease or variations in patient reaction to the same etiology, are grouping them together. Dr. Lever and his group here have done much to establish pemphigus as a separate category.

The pathological classification of these conditions is equally difficult. Two of the diseases that lend themselves readily to histologic differentiation, however, are bullous lupus erythematosus and pemphigus —that is, if the proper biopsy is obtained. In a biopsy taken from a clinically atypical lesion, one with an ulcerated crust or a secondarily infected lesion, the histologic picture is atypical, and the correct diagnosis cannot be made. If there are several different types of lesions several biopsies should be done. Moreover, to differentiate bullous diseases histologically, one must have a biopsy from an early lesion in which there is no secondary necrosis. It is extremely difficult to get a biopsy of a bulla of the mucous membrane; the membrane is friable, and the bulla, which is constantly traumatized by the tongue or food, ruptures at an early stage. I think the physicians who were instrumental in obtaining such a biopsy in this case should be complimented. The biopsy from a clinically typical lesion of bullous lupus erythematosus does not show eosinophils in the corium and does have a reasonably characteristic picture. In all the other bullous diseases there are eosinophils in the corium. In true pemphigus the bullae are usually within the epidermis, with a layer of basal epithelial cells remaining on the floor of the bullae; in addition, acantholytic cells are present in the early lesions.

Many physicians in the past tried to differentiate these diseases on the basis of the position of the bullae in the skin. One group[1] found by serial sections of many of these bullae that the vesicles extended from an intraepidermal to subepidermal location. One of the procedures that have been widely used in this country, particularly in the Philadelphia area, is the Tzanck test, in which the

*Chief of dermatology, Massachusetts Memorial Hospitals.

top of the bulla is removed, the vesicle is blotted with some gauze, and its floor is scraped with a scalpel or a tongue depressor. The scrapings are placed on a slide and stained with Wright or Giemsa stain. If the bulla is a fresh, clean one from a patient with pemphigus, there will be acantholytic cells characterized by destruction of the intercellular bridges, peripheral margination of the chromatin and condensation of the nuclei with a perinuclear halo. Those cells, when present in a bullous disease, are diagnostic of pemphigus; they are not seen in erythema multiforme, epidermolysis bullosa or dermatitis herpetiformis. Occasionally, the cells have been seen in a squamous carcinoma and a few similar conditions. The Tzanck test is also useful in differentiating the bullous diseases due to the intranuclear group of viruses — herpes simplex and varicella — with which there are multinucleated epithelial giant cells that are not present in any other bullous skin disease. On the basis of the skin biopsy I can definitely rule out pemphigus and lupus erythematosus.

Dermatitis herpetiformis is clinically a bullous disease whose cause we do not know. Lately, considerable work has shown that psychogenic factors may be concerned. The disorder usually occurs in young people. Eight patients with dermatitis herpetiformis whom I have recently seen were under psychiatric analysis. Three became psychotic under observation. We know that under hypnosis bullae can be raised on the skin; therefore, it is not beyond the realm of reason to attribute the vesicles of dermatitis herpetiformis to psychogenic factors. Certainly, pruritus, which is the chief complaint, can to a large extent be an expression of tension or other psychogenic factors. This symptom was not present.

Epidermolysis bullosa is in general a lifelong disease. This patient had the disease for only three and a half years, and it began when he was in his seventies.

Erythema multiforme is also a disease for which we do not know one precise etiology. We do know that it occurs in people with drug eruptions, with septic processes or with neoplastic diseases. What the common denominator is we do not know, but we speak glibly in terms of toxins. By definition, erythema multiforme is an acute process and is self-limited. If one accepts that definition, this patient's disease — recurrent bullae and inflammatory disease of the skin for three and a half years — cannot be placed in this classification.

This definition of erythema multiforme includes the syndromes of Behçet, Stevens–Johnson and Reiter, as well as ectodermosis erosiva pleuriorificialis, and excludes dermatitis herpetiformis. There is a great confusion about these diseases, however. If Stevens–Johnson disease is regarded as recurrent it must be removed from this category. This reasoning applies to many of the disorders of the mucous membranes, eye, conjunctiva, urethra, genitals and joints, with bulla formation, in which the histologic picture is the same. If, on the other hand, one defines erythema multiforme as a recurrent bullous disease, there is no justification for not including all the bullous skin diseases except pemphigus. I do not know how justified we are in making these separate entities.

I have narrowed the diagnosis down to pemphigus or pemphigoid. Since histologic sections of bullae of the mouth were obtained, they must have been young bullae; therefore, if this had been pemphigus, the bullae would have been within the epidermis rather than subepidermal, and acantholytic cells would have been present. The skin biopsy confirmed the findings of the mucous-membrane biopsy; therefore, this case is not one of malignant pemphigus. The epithelium of the mucous membrane as far as the cardia of the stomach is the same as the epithelium of the skin for all practical purposes. In these bullous diseases, then, one would expect lesions of the esophagus and at least part of the larynx; occasionally, there are ulcerations of the upper gastrointestinal tract and of the urethra. In pemphigus, and in the other bullous diseases, so far as I have been able to ascertain from the literature, when strictures of the esophagus occur, they are secondary to chronic inflammation, bullae, adhesions or fibrosis with narrowing of the lumen. With that in mind I can restrict this to pemphigoid (benign pemphigus). While I am on this point I should like to say that in these chronic mucous-membrane diseases, at the first sign of narrowing of the esophagus, as evidenced by difficulty in swallowing, visual exploration should be performed to break up the adhesions before scarring of the extent reported in this patient forms. The ulcerations of the conjunctiva, as in this case, may be found in all these diseases. In Stevens–Johnson disease it is slightly more common, being present in about 10 per cent of the cases.

One other point I should like to make is that various medications were used — boric acid compresses, chlortetracycline and so forth. The ACTH and cortisone, of course, are beneficial. The literature suggests that in different eras different medications were supposedly the cure-all for these diseases — the sulfonamides, penicillin, chlortetracycline, streptomycin and so on. The physicians caring for this patient, on several occasions, were courageous enough to use only boric acid compresses, and the lesions subsided.

My diagnosis is pemphigoid, the chronic, bullous mucous-membrane disease, and possibly terminal pneumonia. About 10 per cent of patients with normal skin have beta-hemolytic and 40 per cent coagulase-positive staphylococci; in skin that has broken down 90 per cent have coagulase-positive staphylococci and 40 per cent beta-hemolytic streptococci. This patient's skin was broken down, and

he undoubtedly had these organisms. If he had pneumonia, it was probably caused by one of these organisms.

DR. JOSEPH W. GARDELLA: In 1926 Senear and Usher[2] discussed the simultaneous occurrence of lupus erythematosus and pemphigus; I think it was later called pemphigus erythematosus. Would you like to give any consideration to this?

DR. MESCON: Yes; I did. I did not list it as another group, since as far as I am concerned it is a type of pemphigus and not lupus erythematosus histologically. It is pemphigus, in which the bullous lesions are not prominent, have a seborrheic character and are in a lupus-erythematosus distribution. There have not been enough unequivocal cases yet for me to know whether the L. E. blood test is positive in these cases, but I should guess that it is not.

DR. GARDELLA: In the cases originally described was any histologic evidence of lupus presented?

DR. MESCON: No. The cases originally described we cannot classify today. Pemphigus was not recognized as having a special histologic structure at the time the older cases were reported. Cases that would now undoubtedly be called erythema multiforme, Stevens–Johnson type, might then have been called dermatitis herpetiforme. We often do not know precisely what diseases early writers were talking about.

DR. CHESTER N. FRAZIER: It was our impression that this patient had so-called benign mucous-membrane pemphigus.

CLINICAL DIAGNOSES

Benign mucous-membrane pemphigus.
Esophageal webs.
Aspiration pneumonia.

DR. HERBERT MESCON'S DIAGNOSES

Pemphigoid (benign mucous-membrane pemphigus).
Pneumonia.

ANATOMICAL DIAGNOSES

Benign mucous-membrane pemphigus, skin, eyes, oral mucosa, esophagus.
Chronic esophagitis, with constriction and esophageal web formation.
Conjunctival and corneal fibrosis (blindness).
Aspiration pneumonia, chronic, with fibrosis, severe.
Bronchopneumonia, acute.
Asphyxia due to obstruction of larynx by aspiration.

PATHOLOGICAL DISCUSSION

DR. DAVID KAHN: At autopsy this man was extremely emaciated. The eyelids were scarred shut and could not be forced open. There were a few bullous lesions in the oral cavity, but on the skin only atrophic scars were found on the scalp, face and neck. The most significant findings were in the esophagus and lungs. When we looked into the unopened esophagus from above, a membrane was seen stretched across the lumen at the level of the cricoid cartilage. This membrane was continuous with the mucosa, anteriorly and laterally, and left only a narrow, 0.5-cm. posterior passageway. The membrane was so thin that when we opened the esophagus it shattered into a number of delicate strands attached anteriorly. In the opened state

FIGURE 4.

(Fig. 4) no bullae were found anywhere in the esophagus. The upper 4 cm. of the esophagus above the membrane was normal and measured 3 cm. in circumference. The next 3 cm. was narrowed to 1.5 cm. in circumference, and here the wall was less pliable and somewhat thickened and the mucosa congested and roughened. Below this the esophagus reverted to normal for a distance of 6 cm., at which point a second short segment of constriction, similar to the proximal one but without a membrane formation, was present. Below this second constriction the esophagus was normal.

Microscopical examination of the constricted areas in the esophagus showed a chronic esophagitis, with

fibrosis of the tunica propria and submucosa and, in some areas, with metaplasia of the surface epithelium to a mucus-secreting columnar epithelium. This feature is considered secondary to the chronic irritation of the obstruction, and the finding of hyperkeratosis of areas of the squamous epithelium tends to bear this opinion out. We found no bullae in the esophagus; the lesions were at much the same stage as those in the skin and eyes, the subepidermal scarring from healed bullae being responsible for the damage and residual deformity. The obstructing membrane or esophageal web was a very thin structure consisting of a core of fibrosed tunica propria covered on both sides by normal squamous epithelium; its arrangement suggested that it was formed by adhesions between plaques of regenerating surface mucosa. A section of an oral bullous lesion resembled the surgical biopsy specimen; subepidermal bullae with chronic inflammation and without any evidence of intraepidermal change or acantholysis (Fig. 5).

Lying in the glottis and occluding it and the first part of the larynx was a mass of material 3.5 by 2.5 by 2 cm. with the configuration of a cast of the upper uninvolved esophagus; this represented a bolus of

FIGURE 5.

food formed in the esophagus above the web, which terminally was regurgitated and aspirated into the larynx, resulting in the sudden death.

The lungs weighed 1600 gm. and showed a mixed lesion. They were extremely fibrotic and demonstrated various healing and acute stages of aspiration pneumonia, with a superimposed acute pneumonic process from which pneumococci grew on culture. Aspiration pneumonia, of course, is a common complication of obstructive esophageal lesions.

DR. JOHN F. GIBBONS: I think these films are worth looking at since they show the web in the esophagus two and a half years before the patient died. At that time he had already had evidence of aspiration; the barium is seen in the right-middle-lobe bronchus. A year or so later there were more changes of chronic aspiration pneumonitis in the right lung, and by the time of the final admission there were extensive changes in both lungs, with a great deal of consolidation, shrinkage and fibrosis of the lung, so that these webs had produced aspiration over a period of at least two and a half years.

DR. KAHN: We believe that this case represents benign mucous-membrane pemphigus and the complications that occur secondary to it. Drs. Cogan, Benedict and Lever are going to tell us their experience with the condition.

DR. DAVID COGAN: The eye lesions were typical of so-called benign conjunctival pemphigus occurring

FIGURE 6.

in patients past middle life with an extensive symblepharon connecting the conjunctivas of the lids. We practically never see bullae of the conjunctiva, and rarely do we see any erosions of the conjunctiva. We always see end stages of the bullae, if they exist; yet each time we see the lesions, the symblepharon is slightly worse, so there must be erosions. I have seen only 1 patient among 20 or 30 cases who might have had a bulla of the conjunctiva.

DR. MESCON: The conjunctiva is a relatively thin epithelial membrane. One cannot produce bullae in animals unless their skins are thickened — in other words if one applies a mustard vesicant compound to rabbit skin, vesicles will not appear unless the skin is first thickened with some other chemical. The conjunctiva may react in the same way.

DR. COGAN: One fortunate feature about this is that the cornea is the last to be involved. The disease begins in the fornices of the eye and gradually approaches the cornea. The cornea is usually involved only when the scarring between the lid and globe has been almost complete or when exposure secondary to inability to close the eye develops.

I differ with Dr. Mescon on the identity of the eye findings in erythema multiforme and ocular pemphigus. The end stages are not similar. In ocular pemphigus there is severe ankylosis, which rarely if ever occurs in the erythema-multiforme group. On the other hand with ocular pemphigus in the initial stage there is not the severe exudative conjunctivitis that occurs in erythema multiforme. The prognosis of erythema multiforme is therefore much better as far as the eye is concerned than that of ocular pemphigus.

DR. EDWARD BENEDICT: About a year ago Dr. Walter Lever and I[3] reported 4 cases of stenosis of the esophagus in what we called benign mucous-membrane pemphigus; 1 was the case under discussion today, and I will show a drawing of the esophagus at the time of the esophagoscopy (Fig. 6). There was a web-like structure with a lumen only 3 mm. in diameter right in the center. In another patient, a seventy-one-year-old woman with painful mouth lesions of three years' duration, bilateral conjunctival adhesions for ten years, lesions on the vulva and mucous membranes for ten years and dysphagia for twenty years, an esophagoscopy was done in another hospital for a pea stuck in the esophagus five years before these webs were seen. The x-ray films showed multiple strictures of the esophagus, with fine lesions stretching across the esophagus in a sort of cobweb fashion. By comparison, in stenosis due to acute esophagitis with peptic ulceration, there is reddening, edema and a small lumen, but no web-like structure; in strictures produced by the swallowing of lye the esophagus is fibrosed, with a very rigid type of stenosis. The web-like structures in pemphigus and other types of webs are readily divulsed, but these lesions are not.

DR. WALTER LEVER: Benign mucous-membrane pemphigus, which I prefer to call benign mucous-membrane pemphigoid, is a well defined entity not related to true pemphigus. Originally, the ophthalmologists described it as ocular pemphigus. This name has now been dropped by many because involvement of the conjunctivas, although frequent, is not a necessary part of the disease. The cardinal feature of the disease is bullous lesions on the so-called orificial mucous membranes. Thus, lesions may occur on the conjunctivas, the oral mucosa and the mucous membranes of the larynx, esophagus, nose, penis, vulva and anus. Frequently, these lesions are followed by scarring. About 50 per cent of the patients, like this patient, also have involvement of the skin. The atrophic scarring that takes place both on the skin and mucous membranes never occurs in true pemphigus.

The disease that we call benign mucous-membrane pemphigoid has a nonspecific histologic appearance characterized by subepidermal bullae without the degenerative changes in the epidermis, called acantholysis, that one observes in true pemphigus. There is profound inflammation extending through the entire dermis, resulting in fibrosis. The disease is benign in the sense that it does not have the severe toxic manifestations that we see in true pemphigus. Most of the 30 patients that Dr. Cogan and I have been following are alive. A good number are partially or completely blind, but some have no ocular involvement at all. Only 3 patients have died: 1 with esophageal stenosis, 1 from aspiration bronchopneumonia caused by the tremendous secretion of mucus in the trachea and the patient under discussion.

DR. MESCON: Do you believe that the pemphigoid or benign pemphigus is part of true pemphigus or another pathologic entity?

DR. LEVER: I think it is an entity all by itself and not related to pemphigus.

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GOLDEN-ANNIVERSARY CONGRESS ON MEDICAL EDUCATION AND LICENSURE

SPEAKERS at the fiftieth Annual Congress on Medical Education and Licensure took the opportunity of looking in two directions: backward to the Flexner report and the reformation that it precipitated in 1910, and forward to the possible necessity for another reformation by or before the year 1975. The Congress was attended by 600 medical educators and licensing and specialty-board officials during the three-day meeting in Chicago on February 7, 8 and 9.

The dean of one of the nation's leading medical colleges pointed out that the Government, in fostering international goodwill, is admitting increasingly large numbers of displaced persons, including many physicians about whose professional ability no questions are asked. It was reported that more such physicians will enter New York state this year than will be graduated from all its medical schools, and a member of the New York Board of Medical Examiners called attention to the inadequacy of the medical training of most of the foreign doctors seeking practice in the United States. This migration of physicians has already reached a total of more than 20,000, large numbers of whom have become specialists with no attempt to correct the deficiencies of their basic medical training. It seems that this tendency could quickly and thoroughly undermine the quality of medical practice in the United States.

The secretary of the Council on Medical Education and Hospitals recommended the adoption of a uniform plan for screening the professional competence of foreign-trained physicians. Such a uniform procedure would be of greater assistance to state medical licensing boards than the present attempts to evaluate and list foreign medical schools. Not one in ten of the foreign medical schools provides a basic medical education that is on a par with that of the approved schools in the United States. A careful analysis of state medical-practice acts, with serious consideration of the possible development of a commonly acceptable yardstick or screening mechanism to evaluate the competence of the foreign graduate, was recommended. It was suggested that the National Board of Medical Examiners could be of great help to state boards in determining whether foreign-trained physicians were eligible for further consideration for licensure: the National Board, at the request of a state board, could conduct examinations for professional competency, and the state board could determine whether candidates met other requirements for licensure locally. Lack of uniformity of the various medical-practice acts was commented on, as well as the reluctance of certain state boards to accept the modern type of examination now being conducted by the National Board of Medical Examiners.

A former member of the Nebraska Board of Medical Examiners reviewed recent developments involving a possible recognition of osteopathy, and concluded that the practice of osteopathy always has been and still is a cult. The question of recognizing osteopathy will be placed before the delegates of the American Medical Association for decision at its next annual meeting.

The president of the Advisory Board for Medical Specialties called on the various specialty boards to assume greater leadership in the improvement of medical practice. Altogether, the conference, which was comprehensive, critical and alert to the needs and the challenges of the future, was worthy of a semicentennial.

PRACTICE OF MEDICINE BY MARRIED WOMEN

SHOULD women go into medicine? Probably most people would agree that they should be encouraged to do so if they are properly qualified. Many leading medical schools accept women as candidates for the M.D. degree, and most of these candidates graduate with satisfactory grades. Although these facts do not prove that women are universally successful in medicine, they indicate that they are generally accepted. The more difficult question of matrimony can be categorically answered by the admission that normal family life should not be denied to women in medicine.

The adjustments that married women must make to practice is another matter. Some of those with children have found it impossible to carry on their practices; they cannot find time and strength to do justice to both jobs. Others discover that they can do each job part time. Still others get enough help at home to permit them to devote more time to medicine. This may work out very well, and family life is not sacrificed.

Nowadays, however, the problem of adequate help is a major one. For various reasons, such as the general rise in the American standard of living and social security and unemployment security, most women are not as willing to work in private homes, cooking and taking care of children, as they were in the past. Obviously, they cannot be blamed for this, but the situation as a whole has caused women highly trained in other lines to stay home to do housework, which they often dislike and for which they may not be fitted, whereas women who are perhaps less intelligent and certainly less well educated and who could at least do some housework and take care of children will do neither as a full-time job in a private family.

Although there is no easy solution to this problem a little well placed publicity pointing out that no stigma need be attached to housework or the care of children in a private family would be a step in the desired direction. It might also be mentioned that the wages of such employees usually include board and lodging and are therefore as a rule much higher than those in comparable office or factory work and that such work is obviously to their advantage. It is incumbent on the employer, however, to provide a sufficiently attractive environment, both physically and socially, to make the employment reasonably desirable; any sense of degradation must be entirely removed from domestic service if it is to become an acceptable occupation for modern women. To ease the economic barrier, women in medicine, regardless of whether they are widowed or divorced, — as well as those in other occupations, — might be allowed to deduct the cost of household help from their professional or business incomes.

ECLAMPSIA IN FIJI

IN 1950 Bell and Wills[1] reported a pronounced racial difference in the frequency of eclampsia during pregnancy among indigenous (mainly Melanesian) Fijians and among women of Indian descent who had migrated to Fiji. Forty-five cases of eclampsia were observed in 1522 Indian confinements during a period (1947 through 1949) when no cases were observed in 983 native confinements; no explanation of the facts suggested itself. More recently, Hipsley[2] advanced the hypothesis that the significant difference between the two groups was associated with differences in "fibre" content of the diet. This represented a modification of his earlier concept that lack of dietary magnesium might be the critical factor in causing eclampsia, a theory advanced to explain an observed correspondence between seasonal scarcity of food commodities and seasonal increases of eclampsia in Sydney, Australia.[3]

The fact that magnesium has been found at normal levels in the blood of most toxemic patients[4] makes the latter hypothesis most unlikely. The value of magnesium sulfate injections for controlling eclamptic convulsions appears to lie in its pharmacologic, antispasmodic action — not in its dietetic aspect; Hipsley's present inference is that something associated with the ingested fiber seems to offer protection against the occurrence of eclampsia. A notable epidemiologic characteristic of eclampsia is apparently the comparative freedom from this disorder enjoyed by the peoples of islands in the South Pacific area where fruit and vegetable consumption is high

— in Fiji, New Guinea, the Solomon Islands and Western Samoa.[5]

Bell and Wills, who first called attention to the relative frequency of eclampsia among the two dark-skinned races living side by side in the humid climate of Fiji, also emphasized the necessity for studying amount, equality and constitution of the diets of both groups. Hipsley characterized the Indian diet as one containing flour (sharps), white rice, coconut, oil, ghee and sugar, with small quantities of dhal, meat, milk, vegetables and fruit, and the Fijian diet as having for its staples a starchy fruit-vegetable of which large quantities are eaten, together with bananas, coconut, pawpaw, leafy greens and small quantities of meat, fish and crabs.

Further work along these lines is urgently indicated to clarify the genesis and prevention of eclampsia. The tendency for pre-eclampsia to become evident if the diet is rich in salt and to regress if salt is withheld makes it necessary to ascertain the mineral content of the plant-ash found in food as well as to know more about fiber content.

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RED CROSS FUND

This month the American Red Cross appeals to the nation for the contributions that make possible its program of disaster relief, blood projects, health and safety education, volunteer activities and services to members of the armed forces and their families, as well as to veterans. This year, in addition to the usual annual campaign for funds, enrollment of members is being stressed. Active membership in the Red Cross enables the organization to live up to the citation of President Eisenhower: "We find the Red Cross on duty everywhere ... always true to the belief that people, and only people, matter."

In this section of the country there is little need to emphasize the vital role of the Red Cross in the life of the community. The Worcester tornado last year called forth a tremendous effort to provide food, shelter and first aid to the victims of the disaster; it is well, at this point, to remember that 70 cents of every dollar for this sort of relief is spent in the local community. The availability of blood for emergency transfusions (nearly 40 per cent of all blood for this purpose came from Red Cross services in 1952-53) and for gamma-globulin projects is another important aspect of these activities. Red Cross volunteer assistance in recreation, welfare and rehabilitation in Veterans Administration hospitals is familiar to many in this area. And, finally, the overseas services to members of the nation's military forces are essential to their morale and general well-being.

The American Red Cross holds a unique and enviable position in the estimation of those who are asked, several times each year, to support the campaigns of various philanthropic associations. Conscientious citizens should need no urging to contribute generously and to enroll cheerfully for membership in an organization whose activities are so intimately connected with the general welfare.

The first number of a Medical Journal, called "The Middle States Medical Reformer, and Advocate of Innocuous Medication," has been received.

Boston M. & S. J. *March 22, 1854*

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DEATHS

DONAHUE — Lewis Charles Donahue, M.D., of Needham, died on March 5. He was in his forty-eighth year.

Dr. Donahue received his degree from Tufts College Medical School in 1933, and was a fellow of the American Medical Association.

He is survived by his widow, his mother, two daughters, two sons and a brother.

MORRIS — Ada Bedinger Morris, M.D., of Cambridge, died on February 15. She was in her fortieth year.

Dr. Morris received her degree from the University of Pennsylvania School of Medicine in 1939.

She is survived by her husband, a son, a daughter, a brother and a sister.

BOSTON MEDICAL LIBRARY

PERIPATETIC PHYSICIANS

The Library announces a recent acquisition to its collection of books and pamphlets on the travels of physicians, dating from the fifteenth to the twentieth century. This consists of a series of ten letters written from Paris between December, 1834, and June, 1835, by Dr. Samuel Wigglesworth (Harvard, M.D. 1834) to his father, Thomas Wigglesworth (Harvard, A.M. 1793).

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Pittsfield	March 31*	Edward J. Coughlin, Jr., M.D.
Greenfield	April 1	Charles L. Sturdevant, M.D.
Salem	April 5	Paul W. Hugenberger, M.D.
Gardner	April 6	Carter R. Rowe, M.D.
Haverhill	April 7	William T. Green, M.D.
Brockton	April 8	George W. Van Gorder, M.D.
Lowell	April 9	Albert H. Brewster, M.D.
Lynn†	April 12	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Springfield	April 20	James D. Fisher, M.D.
Hyannis	April 22	Paul L. Norton, M.D.
Worcester	April 23	John W. O'Meara, M.D.
Fall River	April 26	David S. Grice, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	April 6, 13, 20, 27
Fitchburg	April 7, 14, 21, 28

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*Date changed.

†This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

CORRESPONDENCE

PEST AND SYPHILIS

To the Editor: In the "Report of the Librarian" of the Boston Medical Library for 1952, published in the October 22, 1953, issue of the *Journal*, an error occurs on page 687, regarding a book by Johan Widmann, *Regimen in pestilentzischem*, (Strassburg, 1511). This is not a translation of *De pustulis* (1497), as stated, but of *De pestilentia* (Tübingen, after 1500?). The Librarian is indebted to the former librarian of the College of Physicians, Philadelphia, for calling attention to his confusion of pest with syphilis. Pustulis was a pest, but the distinction is clear, and Widmann called his pustulis "mal de franzos," which could only refer to syphilis in 1497.

HENRY R. VIETS, M.D.

Boston

MORE ON PEDICULOSIS CILIORUM

To the Editor: Regarding the letter of Dr. G. H. Flessas, in the December 24 issue of the *Journal*, on pediculosis ciliorum, Dr. Ronchese's rationale in treating pediculosis ciliorum in an infant only by mechanical removal of lice and nits is expressly intended to avoid applying any chemical on an infant eye, whenever possible. D.D.T. is not a harmless substance, and particularly on an infant's eye it could be hazardous. Since cases of pediculosis ciliorum are rare, it would be interesting to know how much experience the United States Typhus Commission has had with infant pediculosis pubis. Sprinkling D.D.T. on the eyelashes would eventually loosen the crabs from their grip, and they would fall, dead or alive. How about the nits? Even if killed would they not stick to the eyelashes until mechanically removed?

BENCEL L. SCHIFF, M.D.

Pawtucket, Rhode Island

REVOCATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held February 25, 1954 it was voted to revoke the registration of Dr. David M. Jones, of Mendon, Massachusetts, because of ill health.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Allergic Patient and His World: Including sources of allergens. By Florence E. Sammis, M.D., M.S.P.H., assistant attending physician in allergy, Nassau Hospital, Mineola, New York. With pollen charts, maps and photographs by Oren C. Durham, chief botanist, Abbott Laboratories, North Chicago, Illinois. 8°, cloth, 156 pp., with 12 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $4.75. (Publication No. 157, *American Lecture Series.*)

Dr. Sammis has written this book especially for persons with allergic conditions. There are special chapters on hay fever, bronchial asthma, food allergy, allergy of the skin and elimination diets and special instructions and recipes. An appendix lists the ingredients of commercial breads and salad oils. There is a bibliography of 4-1/2 pages and an index. This practical book should be in all collections on allergy and available to all allergists.

Antibiotics. By Robertson Pratt, Ph.D., professor of pharmacognosy and plant physiology, University of California College of Pharmacy, and consultant on antibiotics; and Jean Dufrenoy, D.Sc.(Paris), research associate in antibiotics, University of California College of Pharmacy. Second edition. 8°, cloth, 398 pp., with 87 illustrations. Philadelphia: J. B. Lippincott Company, 1953. $7.50.

This standard book has been revised and brought up to date since the publishing of the first edition in 1949. The text has been divided into four parts, on fundamental, industrial and applied aspects, and the modification of biologic and social systems. The section on applied aspects comprises 206 pages, and the various antibiotics are discussed separately and at length; there are chapters on mixed therapy and on antibiotics in dental and oral surgery and in agriculture. Lists of references are appended to the chapters, and there is a good index. The book should be in collections on the subject.

NOTICES

BOSTON CITY HOSPITAL ALUMNI ASSOCIATION

The Alumni Association clinical meetings of the Boston City Hospital will be held at the hospital on April 24, starting at 9 a.m. The programs are as follows:

Medical. Cheever Amphitheater. Dr. John P. Rattigan presiding.

Surgical. Amphitheater, Mallory Institute of Pathology. Dr. John J. Byrne presiding.

Orthopedic. Shortell Unit. Dr. Augustine W. Eddy presiding.

MEDICAL LIBRARY ASSOCIATION

The fifty-third annual meeting of the Medical Library Association will be held at the Hotel Statler, Washington, D. C., June 15 through 18. The Armed Forces Medical Library will be host. Among the speakers will be Dr. Detlev Bronk, president, Rockefeller Institute of Medical Research; Lieutenant Colonel Frank B. Rogers, director, Armed Forces Medical Library; Verner Clapp, acting Librarian of Congress; and Dr. Raymond Zwemer, chief, Science Division, Library of Congress. Further information may be obtained from Lieutenant Colonel Frank B. Rogers, Armed Forces Medical Library, 7th Street and Independence Avenue, S.W., Washington 25, D.C.

INSTITUTE OF INDUSTRIAL HEALTH

A symposium on fluorides will be presented by the Kettering Laboratory in the Department of Preventive Medicine and Industrial Health of the University of Cincinnati under the auspices of the Institute of Industrial Health, May 10 through 12. Application blanks for the course may be obtained from the Secretary, Institute of Industrial Health, Kettering Laboratory, Eden and Bethesda Avenues, Cincinnati 19, Ohio. Attendance will be limited in number.

NEW YORK ACADEMY OF MEDICINE EASTERN STATES HEALTH-EDUCATION CONFERENCE

The 1954 Eastern States Health-Education Conference of the New York Academy of Medicine will be held at the Academy on April 29 and 30. The subject of the conference will be communication in health education. Among the speakers will be professors William McPhee and Elihu Katz, Bureau of Applied Social Research, and Dean Louis Hacker, School of General Studies, Columbia University; Dr. Leo Lowenthal, Voice of America; Dr. Shirley A. Star, National Opinion Research Center, University of Chicago; and Professor Earl L. Koos, School of Social Welfare, Florida State University. Participation is limited. Further information may be obtained from Iago Galdston, M.D., New York Academy of Medicine, 2 East 103 Street, New York 29, New York.

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

The twelfth regular meeting of the New York Society for Circulatory Diseases will be held in room 440 of the New York Academy of Medicine, New York City, on April 13 at 8:30 p.m. The meeting will be devoted to a symposium on the subject "Surgery of Acquired Heart Disease." Drs. O. Henry Janton, Jr., and Robert P. Glover, Presbyterian Hospital, Philadelphia, will speak on the topics "Pertinent Prognostic Factors in Selection of Patients with Acquired Heart Disease for Surgery" and "Present Status of Surgery for Acquired Heart Disease," respectively.

INTERNATIONAL COLLEGE OF SURGEONS

The ninth biennial congress of the International College of Surgeons will be held in Sao Pāulo, Brazil, April 26 to May 2, in conjunction with the fourth centennial of the city, at the invitation of the Governor. The central theme of the congress will be "Government Controlled Medicine," and the principal speakers will be Professor Cesarino, Jr., University of Sao Pāulo, and Drs. Edward J. McCormick, president, and David B. Allman, representative, of the American Medical Association, respectively.

INTERNATIONAL COLLEGE OF SURGEONS EXAMINATIONS

Qualifying examinations for fellowship in the International College of Surgeons will be held in Chicago on May 3 and 4. Written examination will be given at Cook County Graduate School of Medicine, 707 South Wood Street, on May 3, and the clinical examinations at Cook County Hospital on May 4.

SOCIETY MEETINGS AND CONFERENCES

March 22. Phi Delta Epsilon Fraternity Graduate Club of Boston. Page 399, issue of March 4.

March 22–25. American Academy of General Practice. Page 129, issue of January 21.

March 22–31. Consultation Clinics for Crippled Children. Page 303, issue of February 18.

March 24. Middlesex East District Medical Society.

March 24. Boston Committee on Alcoholism. Page 443, issue of March 11.

March 26–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

March 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

March 28. National Gastroenterological Association. Page 265, issue of February 11.

March 31. Boston City Hospital Seminar on Peripheral Disease. Page 443, issue of March 11.

March 31. Tufts Medical Alumni Dinner Meeting. Page 443, issue of March 11.

March 31–April 2. American College of Surgeons. Sectional Meeting. Page 266, issue of February 11.

March 31–April 28. Consultation Clinics for Crippled Children. Page 490.

April 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

April 7. Massachusetts Academy of General Practice. Page 443, issue of March 11.

April 8–11. International Academy of Proctology. Page 130, issue of January 21.

April 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

April 9. New England Society of Anesthesiologists. Page 399, issue of March 4.

April 10. American Congress of Physical Medicine. Page 266, issue of February 11.

April 13. New York Society for Circulatory Diseases. Page 491.

April 17 and May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.

April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

April 21–24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.

April 24. Boston City Hospital Alumni Association. Page 491.

April 26–May 2. International College of Surgeons. Notice above.

April 29 and 30. New York Academy of Medicine. Eastern States Health Education Conference. Page 491.

April 29, 30 and May 1. American Goiter Association. Hotel Somerset, Boston.

May 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.

May 10–12. Institute of Industrial Health. Page 491.

May 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.

June 13–17. American Society of Medical Technologists. Page 444, issue of March 11.

June 15–18. Medical Library Association. Page 491.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 25

THURSDAY, MARCH 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m. Thoracic Conference. Suppurative Diseases of the Lung. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Dermatologic Histochemistry of Value to the Internist and Surgeon. Dr. Herbert Mescon. Stearns Auditorium, New England Center Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MARCH 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Drs. Proger, Hayman, McCombs, Astwood and other members of the Medical Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

4:00 p.m. Boston Lying-in Hospital Journal Club. Disorders in the Involution of the Placental Site. Dr. Hugh Grady. Boston Lying-in Hospital Auditorium, 221 Longwood Avenue.

4:00–5:00 p.m. Boston Lying-in Hospital Journal Club. Cancer of the Colon. Dr. Arthur W. Allen. Auditorium, Boston Lying-in Hospital.

*4:00–6:00 p.m. X-Ray Conference. Dr. Edward B. D. Neuhauser. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, MARCH 27

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek, Pratt Auditorium, New England Center Hospital.

MONDAY, MARCH 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff, Cheever Amphitheater, Dowling Building, Boston City Hospital.

(Notices concluded on page xxiii)